

Exhibit 21

1 IN THE UNITED STATES DISTRICT COURT
2 FOR THE EASTERN DISTRICT OF NEW JERSEY

3 - - -

4
5 IN RE: JOHNSON & :
6 JOHNSON TALCUM POWDER :
7 PRODUCTS MARKETING, :
8 SALES PRACTICES, AND : NO. 16-2738
9 PRODUCTS LIABILITY : (FLW) (LHG)
10 LITIGATION :
11 :
12 THIS DOCUMENT RELATES :
13 TO ALL CASES :

14 - - -

15 January 21, 2019

16 - - -

17 Videotaped deposition of
18 JUDITH ZELIKOFF Ph.D., taken pursuant to
19 notice, was held at the Sheraton Mahwah
20 Hotel, 1 International Boulevard, Mahwah,
21 New Jersey, beginning at 9:11 a.m., on
22 the above date, before Michelle L. Gray,
23 a Registered Professional Reporter,
24 Certified Shorthand Reporter, Certified
 Realtime Reporter, and Notary Public.

 - - -

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VIDEOTAPE TECHNICIAN:
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I N D E X

Testimony of: JUDITH ZELIKOFF, Ph.D.

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By Mr. Ferguson 442

By Ms. O'Dell 486, 571

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1	- - -		1	- - -	
2	E X H I B I T S (Cont'd.)		2	DEPOSITION SUPPORT INDEX	
3	- - -		3	- - -	
4			4		
5	NO.	DESCRIPTION	5	Direction to Witness Not to Answer	
6	Zelikoff-38	Talcum Powder	6	PAGE	LINE
7		Chronic Pelvic		None.	
8		Inflammation	7		
9	Zelikoff-39	Markers of	8	Request for Production of Documents	
10		Inflammation	9	PAGE	LINE
11		And Risk		None.	
12		(Wu)	10		
13	Zelikoff-40	Binder Labeled	11	Stipulations	
14		Saad 2010 -	12	PAGE	LINE
15		Zambelli 2013		None.	
16	Zelikoff-41	Binder Labeled	13		
17		Production Documents	14	Questions Marked	
18	Zelikoff-42	Binder Labeled	15	PAGE	LINE
19		Depositions		None.	
20		ACGIH 2010 -	16		
21		Frank & Jorge 2011	17		
22	Zelikoff-43	Binder Labeled	18		
23		IARC 1977 -	19		
24		IARC 2006	20		
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		Ingersoll 2011 -			
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1	- - -		1	THE VIDEOGRAPHER: We are on	
2	E X H I B I T S (Cont'd.)		2	the record. My name is Henry	
3	- - -		3	Marte. I am a videographer with	
4			4	Golkow Litigation Services.	
5	NO.	DESCRIPTION	5	Today is January 21st, 2019,	
6	Zelikoff-46	Binder Labeled	6	and the time is 9:11 a.m.	
7		Mattenklott 2007 -	7	This video deposition is	
8	Zelikoff-47	Binder Labeled	8	being held in Mahwah, New Jersey,	
9		IARC 2009 -	9	in the matter of Talcum Powder	
10	Zelikoff-48	Alterations in	10	Litigation.	
11		Gene Expression	11	The deponent today is Dr.	
12		In Human Mesothelial	12	Judith Zelikoff.	
13		Cells	13	All appearances will be	
14		(Shukla)	14	noted on the stenographic record.	
15	Zelikoff-49	Experts of Transcript 549	15	Will the court reporter please	
16		Of Robert Glenn	16	administer the oath to the	
17		10/18/18	17	witness.	
18	Zelikoff-50	Presence of	18	- - -	
19		Talc in Pelvic	19	... JUDITH ZELIKOFF, Ph.D.,	
20		Lymph Nodes of a Woman	20	having been first duly sworn, was	
21		(Cramer)	21	examined and testified as follows:	
22	Zelikoff-51	Does Long-Term	22	- - -	
23		Talc Exposure	23	EXAMINATION	
24		Have a Carcinogenic	24	- - -	
		Effect			
		(Keskin)			

<p style="text-align: right;">Page 14</p> <p>1 BY MR. HEGARTY:</p> <p>2 Q. Good morning, Dr. Zelikoff.</p> <p>3 A. Good morning.</p> <p>4 Q. My name is Mark Hegarty. I</p> <p>5 represent the J&J defendants in this</p> <p>6 action. Can you please state your full</p> <p>7 name for the record, please?</p> <p>8 A. Judith Terri Zelikoff.</p> <p>9 Q. Dr. Zelikoff, who is your</p> <p>10 current employer?</p> <p>11 A. New York University School</p> <p>12 of Medicine, also known as NYU Langone</p> <p>13 Health.</p> <p>14 Q. What is your title at New</p> <p>15 York University School of Medicine?</p> <p>16 A. Professor with tenure.</p> <p>17 Q. How long have you held that</p> <p>18 position?</p> <p>19 A. Since 1982.</p> <p>20 Q. Do you have any separate</p> <p>21 personal consulting business for</p> <p>22 litigation purposes?</p> <p>23 A. I do not.</p> <p>24 Q. Where do the fees go that</p>	<p style="text-align: right;">Page 16</p> <p>1 plaintiffs' counsel for your services in</p> <p>2 this litigation?</p> <p>3 A. \$350 per hour.</p> <p>4 Q. Is there any difference in</p> <p>5 your rate depending on whether it's</p> <p>6 literature review, sitting for a</p> <p>7 deposition, trial testimony?</p> <p>8 A. Sitting for a deposition or</p> <p>9 trial testimony is \$450.</p> <p>10 Q. Did anyone outside of</p> <p>11 plaintiffs' attorneys assist you in any</p> <p>12 way with your expert report in this case?</p> <p>13 A. No one with my expert</p> <p>14 report.</p> <p>15 Q. We were provided today a</p> <p>16 copy of several invoices that you have</p> <p>17 prepared for your work in this case. I'm</p> <p>18 going to mark as Exhibit Number 1 a copy</p> <p>19 of those invoices.</p> <p>20 (Document marked for</p> <p>21 identification as Exhibit</p> <p>22 Zelikoff-1.)</p> <p>23 BY MR. HEGARTY:</p> <p>24 Q. Dr. Zelikoff, would you look</p>
<p style="text-align: right;">Page 15</p> <p>1 you earn as an expert witness in this</p> <p>2 case?</p> <p>3 A. They go to household</p> <p>4 expenses as well as charity.</p> <p>5 Q. But they go to you, correct?</p> <p>6 A. They go to me.</p> <p>7 Q. Other than your work at New</p> <p>8 York University and the fees that you're</p> <p>9 earning as part of this litigation, do</p> <p>10 you have any other sources of income?</p> <p>11 A. Just income that I have from</p> <p>12 advisory boards or -- when you -- when</p> <p>13 you sit on panels, they also pay you.</p> <p>14 But other than that, no.</p> <p>15 Q. Tell me an example of an</p> <p>16 advisory board for which you receive</p> <p>17 income.</p> <p>18 A. It's on a very sporadic</p> <p>19 basis. And it depends on what it is.</p> <p>20 But the NIEHS, National Institute of</p> <p>21 Environmental Health Sciences. And it's</p> <p>22 an NIH institute. And I serve as a -- I</p> <p>23 review grants for them.</p> <p>24 Q. What are you charging</p>	<p style="text-align: right;">Page 17</p> <p>1 at Exhibit Number 1 and tell me whether</p> <p>2 those are all the invoices that you have</p> <p>3 generated and provided to plaintiffs'</p> <p>4 counsel in this case.</p> <p>5 A. It appears to be.</p> <p>6 Q. Thank you. The last work</p> <p>7 noted is December 24, 2018.</p> <p>8 Have you spent any</p> <p>9 additional time on this case for which</p> <p>10 you intend to bill plaintiffs' counsel --</p> <p>11 A. Yes, I have.</p> <p>12 Q. -- that's not reflected in</p> <p>13 the invoices?</p> <p>14 A. Yes, I have.</p> <p>15 Q. How much additional time?</p> <p>16 A. Approximately 25 to 30 hours</p> <p>17 by the end of this deposition. Not</p> <p>18 including the deposition.</p> <p>19 Q. With regard to these</p> <p>20 invoices, have they all been paid?</p> <p>21 A. Yes, they have.</p> <p>22 Q. Were you paid a retainer for</p> <p>23 your work on this case?</p> <p>24 A. I don't recall.</p>

<p style="text-align: right;">Page 18</p> <p>1 Q. Dr. Zelickoff, as you know 2 we're here to take your deposition in the 3 case of In Re Johnson & Johnson Talc 4 Litigation, which is an MDL setting. Are 5 you aware you've been designated as an 6 expert in that case? 7 A. I am aware. 8 Q. When were you first 9 contacted about serving as an expert in 10 this case? 11 A. Early 2017. I was 12 requested -- I was requested if I had 13 interest in it. 14 Q. The first invoice that you 15 provided has a date of April 5, 2017. 16 When in relation to the first invoice 17 entry was that initial contact? 18 A. To the best of my knowledge, 19 it was January or February. 20 Q. Of 2017? 21 A. Of 2017, right. 22 Q. Who contacted you? 23 A. Jennifer Emmel. 24 Q. Did you know her before she</p>	<p style="text-align: right;">Page 20</p> <p>1 representing plaintiffs? 2 A. No, sir. 3 Q. Did you agree to serve as an 4 expert witness at the time of Ms. Emmel's 5 first contact with you? 6 A. No, sir. I told her that I 7 would have to do some literature 8 searching myself and come up with a 9 conclusion as to whether or not I felt 10 comfortable based on the science in 11 serving in that capacity. 12 Q. At one point -- at what 13 point between -- at what point did you 14 come to or did -- strike that. 15 At what point did you agree 16 to serve as an expert witness in this 17 litigation in relation to that first 18 call? 19 A. Probably about a month 20 later. 21 Q. What did Ms. Emmel tell you 22 at that first call about the litigation? 23 MS. O'DELL: We just 24 instruct -- I mean conversations,</p>
<p style="text-align: right;">Page 19</p> <p>1 contacted you? 2 A. Not at all. 3 Q. How was the contact made, by 4 telephone? 5 A. By telephone. 6 Q. Apart from anything that 7 attorneys for plaintiffs may have told 8 you, do you know how she came to contact 9 you? 10 A. I'm not aware as to how she 11 came to contact me. 12 Q. Did you have any prior 13 litigation work with her? 14 A. Not with Ms. Emmel, no. 15 Q. How do you spell her name? 16 A. How do I -- 17 Q. Yes. 18 A. -- spell her name? 19 Q. Yes. 20 A. To the best of my knowledge, 21 it's E-M-M-E-L. 22 Q. Have you had any prior 23 litigation work with any of the lawyers 24 with whom you have met that are</p>	<p style="text-align: right;">Page 21</p> <p>1 in terms of -- let me just strike 2 that and say don't discuss 3 anything that you communicated to 4 us or we communicated to you after 5 you decided to become an expert in 6 the case. 7 BY MR. HEGARTY: 8 Q. Correct. I'm talking about, 9 right now I'm talking about that initial 10 phone call where you said you had not -- 11 where you did not agree at that point in 12 time to serve as an expert witness. 13 That's the only call I'm talking about. 14 What did Ms. Emmel tell you 15 about the litigation or about what they 16 wanted you to do at that first call? 17 A. Well, I don't remember the 18 details as it was about over a year ago. 19 But to the best of my knowledge and my 20 recollection, it was just that they 21 represented the plaintiffs in a case of 22 ovarian cancer and its relationship to 23 talcum powder products, and was I 24 familiar with it, did I know anything</p>

<p style="text-align: right;">Page 22</p> <p>1 about it, and did I have -- did I have 2 interest in being associated with, and I 3 responded to her that I follow the 4 science, that's all I do is I follow the 5 science. 6 And if the science leads me 7 in a direction that I would have interest 8 or that I felt comfortable in doing this, 9 then I would let her know. 10 Q. What was your response when 11 she asked you if you were familiar with 12 the science of talc and ovarian cancer? 13 A. I was familiar with it at 14 that time in a superficial manner. I 15 work in a very high-powered department of 16 environmental medicine. And we discuss 17 current events over lunch. 18 Q. When you say in a 19 superficial manner, what do you mean? 20 A. Certainly not to the depth 21 that I'm aware of the issue currently. 22 Q. Is it correct that you had 23 not formed any opinions as to any link 24 between talc and ovarian cancer as of the</p>	<p style="text-align: right;">Page 24</p> <p>1 the time that you agreed to serve as an 2 expert witness in the case? 3 A. No, not -- not to my 4 recollection. 5 Q. Do you recall anything else 6 that you discussed with Ms. Emmel at that 7 first call besides what we talked about 8 already? 9 A. No, sir. 10 Q. Did Ms. Emmel at that first 11 call tell you anything about plaintiffs' 12 theory of causation or theory of 13 mechanism of action or biologic 14 plausibility? 15 A. No, sir, not at all. 16 Q. Did she send you any 17 documents before you agreed to serve as 18 an expert witness? 19 A. Not to my knowledge. I 20 think the -- I'm sure the literature 21 reviews that I did at that time were 22 solely my own. 23 Q. Had you heard of lawsuits 24 involving talc and ovarian cancer before</p>
<p style="text-align: right;">Page 23</p> <p>1 time of that first call with Ms. Emmel? 2 A. I had -- I had no opinion at 3 that time. 4 Q. Did you have any discussions 5 with Ms. Emmel or any other lawyer 6 representing plaintiffs between that 7 initial phone call and when you agreed to 8 serve as an expert witness? 9 A. To my -- to the best of my 10 knowledge, I had not spoken to 11 Ms. O'Dell. So to the best of my 12 knowledge it was just Ms. Emmel. 13 Q. Again, focusing on that 14 first phone call -- well, strike that. 15 Had you had any further 16 discussion with Ms. Emmel between the 17 time of that first call and the time you 18 agreed to serve as an expert witness? 19 A. I'm sorry, between the time 20 of the first call and the time I agreed, 21 could you repeat the question please? 22 Q. Sure. Did you have any 23 additional discussions with Ms. Emmel 24 between the time of the first call and</p>	<p style="text-align: right;">Page 25</p> <p>1 being contacted by Ms. Emmel? 2 A. I actually had not. 3 Q. What then were your sources 4 of knowledge about talc and ovarian 5 cancer as of the time of the first call? 6 A. The media, whatever I might 7 have read in the paper and any 8 discussions that might have been brought 9 up by my colleagues. 10 Q. Do you recall any colleague 11 who brought the -- anything up about talc 12 and ovarian cancer? 13 A. I do not recall a specific 14 colleague. Lunchroom chatter. 15 Q. Did you form any opinions 16 from the material you did read in the 17 media or from discussion with your 18 colleagues? 19 A. I had no opinion. 20 Q. And you were ultimately 21 retained and asked to give expert 22 opinions in this case, correct? 23 A. I was ultimately retained, 24 yes, correct.</p>

<p style="text-align: right;">Page 26</p> <p>1 Q. The lawyers for the</p> <p>2 plaintiffs in this case have paid you to</p> <p>3 review materials and offer opinions,</p> <p>4 correct?</p> <p>5 MS. O'DELL: Objection to</p> <p>6 the form.</p> <p>7 THE WITNESS: Do I answer</p> <p>8 the question?</p> <p>9 BY MR. HEGARTY:</p> <p>10 Q. Yes.</p> <p>11 MS. O'DELL: Yes.</p> <p>12 THE WITNESS: They have</p> <p>13 remunerated me for my time and</p> <p>14 effort in reading hundreds of</p> <p>15 articles.</p> <p>16 BY MR. HEGARTY:</p> <p>17 Q. The opinions that you've</p> <p>18 formulated were ultimately set out in</p> <p>19 your November 16, 2018, MDL report,</p> <p>20 correct?</p> <p>21 A. That's correct.</p> <p>22 Q. The hours you spent in</p> <p>23 preparing that report are reflected in</p> <p>24 the invoices we marked as Exhibit</p>	<p style="text-align: right;">Page 28</p> <p>1 testify today?</p> <p>2 A. It would be in my invoice,</p> <p>3 but if I had to approximate that without</p> <p>4 the knowledge of having that in front of</p> <p>5 me, I would say 30 to 50 hours.</p> <p>6 Q. What attorneys did you meet</p> <p>7 with to prepare for your deposition here</p> <p>8 today?</p> <p>9 A. I met with Ms. O'Dell and</p> <p>10 Ms. Emmel.</p> <p>11 Q. Anyone else?</p> <p>12 A. In a face-to-face.</p> <p>13 Q. Face-to-face. There were</p> <p>14 phone calls as well?</p> <p>15 A. There were -- one of -- one</p> <p>16 of the phone calls, it may have been two.</p> <p>17 I also -- Chris, and I'm not familiar</p> <p>18 with your last name, sorry.</p> <p>19 Chris from the --</p> <p>20 MS. O'DELL: Tisi.</p> <p>21 THE WITNESS: Tisi? Chris</p> <p>22 Tisi and Alistair --</p> <p>23 MR. FINDEIS: Findeis.</p> <p>24 MS. O'DELL: Findeis.</p>
<p style="text-align: right;">Page 27</p> <p>1 Number 1, correct?</p> <p>2 A. I don't recall what exhibit</p> <p>3 number it is, but it is in one of the</p> <p>4 invoices.</p> <p>5 Q. A description that you have</p> <p>6 in your invoices includes report</p> <p>7 preparation. Is that a description which</p> <p>8 describes your -- the time you spent</p> <p>9 preparing your report?</p> <p>10 A. Yes, it is.</p> <p>11 Q. Every entry under report</p> <p>12 preparation would be the time that you</p> <p>13 spent preparing your report?</p> <p>14 A. Yes, that's true. That</p> <p>15 could include reading material, searching</p> <p>16 for material or writing.</p> <p>17 Q. The invoices we marked as an</p> <p>18 exhibit also reflect the time you spent</p> <p>19 with lawyers for plaintiffs; is that</p> <p>20 correct?</p> <p>21 A. It does.</p> <p>22 Q. With regard to your</p> <p>23 deposition here today, how much time did</p> <p>24 you spend preparing to come here and</p>	<p style="text-align: right;">Page 29</p> <p>1 THE WITNESS: Findeis -- was</p> <p>2 on the phone, and there may have</p> <p>3 been one or two others, but I</p> <p>4 don't recall.</p> <p>5 BY MR. HEGARTY:</p> <p>6 Q. Have you spoken with any of</p> <p>7 your colleagues about your work in this</p> <p>8 litigation?</p> <p>9 A. What -- can you explain what</p> <p>10 you mean by colleagues?</p> <p>11 Q. Well, you mentioned</p> <p>12 colleagues in discussing talc and ovarian</p> <p>13 cancer. So those colleagues.</p> <p>14 A. If -- do you mean other</p> <p>15 faculty?</p> <p>16 Q. Correct.</p> <p>17 A. And the question again,</p> <p>18 please?</p> <p>19 Q. Sure. Have you spoken with</p> <p>20 other faculty at New York University</p> <p>21 regarding your work on this litigation?</p> <p>22 A. No, I have not.</p> <p>23 Q. Have you told any faculty at</p> <p>24 New York University of your opinions in</p>

<p style="text-align: right;">Page 30</p> <p>1 this case?</p> <p>2 A. I have not.</p> <p>3 Q. Have you told anyone at NYU</p> <p>4 School of Medicine of your opinions?</p> <p>5 A. I have not. I have</p> <p>6 discussed, not my opinion, but in my</p> <p>7 class, my toxicology course, to graduate</p> <p>8 students at NYU.</p> <p>9 I have, in my course on</p> <p>10 speaking about reproductive toxicology</p> <p>11 and developmental toxicology, in</p> <p>12 discussing risk factors, two graduate</p> <p>13 students I have discussed -- I've</p> <p>14 included talc as a potential risk factor.</p> <p>15 Q. When did you start including</p> <p>16 talc as a potential risk factor in that</p> <p>17 course?</p> <p>18 A. Prior -- if you're asking me</p> <p>19 was it prior to or -- prior to my</p> <p>20 retainment, it was prior to my</p> <p>21 retainment.</p> <p>22 Q. So prior to your</p> <p>23 retainment -- let me -- let me word it</p> <p>24 differently.</p>	<p style="text-align: right;">Page 32</p> <p>1 A. Yes.</p> <p>2 Q. Does that continue to be the</p> <p>3 extent of any discussion you had with any</p> <p>4 students at New York University about</p> <p>5 talc and ovarian cancer?</p> <p>6 A. Well, right now we're on</p> <p>7 break. I -- I probably will -- I will</p> <p>8 continue after the deposition to also</p> <p>9 talk -- talk with them and list it as</p> <p>10 a -- as a risk factor for ovarian cancer.</p> <p>11 Q. What about -- strike that.</p> <p>12 Did you have discussions,</p> <p>13 that same discussion with toxicology</p> <p>14 students between -- I should say before</p> <p>15 you were contacted by Ms. Emmel and</p> <p>16 today, have you had -- continued to have</p> <p>17 that same discussion with your toxicology</p> <p>18 students?</p> <p>19 A. I've not --</p> <p>20 MS. O'DELL: Objection to</p> <p>21 form.</p> <p>22 Doctor, give me just a</p> <p>23 moment after the question if I</p> <p>24 need to object. Thank you.</p>
<p style="text-align: right;">Page 31</p> <p>1 Prior to the call from</p> <p>2 Ms. Emmel, you had included in your</p> <p>3 course to -- your toxicology course a</p> <p>4 discussion about talc and ovarian cancer?</p> <p>5 A. Not a discussion, just</p> <p>6 didactic lecture saying that this is the</p> <p>7 female reproductive tract. Ovarian</p> <p>8 cancer is part of an adverse outcome of</p> <p>9 disease. It's very prevalent. And there</p> <p>10 are factors including early menarche,</p> <p>11 late menopause, and there's some issues</p> <p>12 currently on the table as to whether</p> <p>13 cosmetic talc also plays a role.</p> <p>14 No opinion was given to my</p> <p>15 class. Just information.</p> <p>16 Q. Do you have any materials</p> <p>17 for your course, whether in PowerPoint</p> <p>18 form or other form that sets out that</p> <p>19 discussion you just had?</p> <p>20 A. No.</p> <p>21 Q. Is that the extent of the</p> <p>22 discussion that you had with your</p> <p>23 toxicology students about talc and</p> <p>24 ovarian cancer?</p>	<p style="text-align: right;">Page 33</p> <p>1 THE WITNESS: Shall I</p> <p>2 continue?</p> <p>3 BY MR. HEGARTY:</p> <p>4 Q. Sure.</p> <p>5 A. Could you repeat the</p> <p>6 question, please?</p> <p>7 Q. Sure. You mentioned that</p> <p>8 the discussion that we just went over was</p> <p>9 before your contact by Ms. Emmel,</p> <p>10 correct?</p> <p>11 A. I said that it started. My</p> <p>12 lectures started prior to my conversation</p> <p>13 with Ms. Emmel.</p> <p>14 Q. What was -- what was the</p> <p>15 name of the course that you had that</p> <p>16 lecture?</p> <p>17 A. Organ system toxicology.</p> <p>18 Q. Have you taught that course</p> <p>19 since your call with Ms. Emmel?</p> <p>20 A. Actually it's coming up</p> <p>21 this -- this semester, starting the 30th</p> <p>22 of January.</p> <p>23 Q. So between -- as of the</p> <p>24 first part of 2017 through today you have</p>

<p style="text-align: right;">Page 34</p> <p>1 not taught that same course?</p> <p>2 A. It's taught every other</p> <p>3 year.</p> <p>4 Q. Have you communicated with</p> <p>5 anyone outside of plaintiffs' counsel in</p> <p>6 this case about your opinions in your</p> <p>7 report?</p> <p>8 A. Not about my opinions, no.</p> <p>9 Q. Have you talked with anyone</p> <p>10 outside of plaintiffs' counsel in this</p> <p>11 case about your report?</p> <p>12 A. Only to say that I -- to my</p> <p>13 friends, when I refuse to go anywhere</p> <p>14 with them, because I have to stay home</p> <p>15 and work, only to say that I'm working on</p> <p>16 a report.</p> <p>17 Q. Have you discussed the</p> <p>18 litigation or your report with any other</p> <p>19 experts retained by the plaintiffs in</p> <p>20 this case?</p> <p>21 A. No, sir, I have not.</p> <p>22 Q. Have you reviewed any of the</p> <p>23 other plaintiffs' experts' MDL reports in</p> <p>24 this litigation besides those referenced</p>	<p style="text-align: right;">Page 36</p> <p>1 Exhibit B. It should be the very last</p> <p>2 page of that document.</p> <p>3 A. Thank you.</p> <p>4 Q. The very last page of</p> <p>5 Exhibit B of your report, you list a</p> <p>6 number of expert reports, correct?</p> <p>7 A. I do. Deposition and</p> <p>8 exhibits.</p> <p>9 Q. Have you reviewed any other</p> <p>10 expert reports -- strike that.</p> <p>11 Did you review any other</p> <p>12 expert reports for purposes of your</p> <p>13 expert report besides those listed here?</p> <p>14 A. No, sir. Unless --</p> <p>15 Dr. Longo, December 2018 supplement, that</p> <p>16 was a report, and I did review that.</p> <p>17 Q. We were provided today with</p> <p>18 a copy of a report of Longo and Rigler,</p> <p>19 January 15, 2019. And I'm going to mark</p> <p>20 that as Exhibit 3.</p> <p>21 (Document marked for</p> <p>22 identification as Exhibit</p> <p>23 Zelikoff-3.)</p> <p>24 BY MR. HEGARTY:</p>
<p style="text-align: right;">Page 35</p> <p>1 in your report?</p> <p>2 A. I reviewed Dr. Dydek's. I</p> <p>3 reviewed -- did you say the plaintiffs'</p> <p>4 witnesses?</p> <p>5 Q. Yeah, let me -- let me -- in</p> <p>6 your report -- and I can -- we can get it</p> <p>7 out here in a moment. But you list</p> <p>8 the -- in your list of reports, you list</p> <p>9 the report of Michael Crowley.</p> <p>10 A. I'm sorry, sir. Can you --</p> <p>11 Q. It's in Exhibit B at the end</p> <p>12 of Exhibit B of your report. If you need</p> <p>13 a copy I can give it to you now.</p> <p>14 A. Can you give me a copy.</p> <p>15 (Document marked for</p> <p>16 identification as Exhibit</p> <p>17 Zelikoff-2.)</p> <p>18 BY MR. HEGARTY:</p> <p>19 Q. I'm marking Exhibit 2 Dr.</p> <p>20 Zelikoff's report that was provided to us</p> <p>21 in this case.</p> <p>22 A. Thank you. And what page</p> <p>23 are you referring to?</p> <p>24 Q. It is the last page of</p>	<p style="text-align: right;">Page 37</p> <p>1 Q. Is that the supplemental</p> <p>2 report that you described for us?</p> <p>3 A. It is, sir. It's an</p> <p>4 analysis Johnson & Johnson Historical</p> <p>5 Product Containers and Imerys' Historical</p> <p>6 Railroad Car Samples, etc..</p> <p>7 Q. That report is dated</p> <p>8 January 15th, 2019, correct?</p> <p>9 A. Yes, sir.</p> <p>10 Q. When did you receive this</p> <p>11 report?</p> <p>12 A. In January.</p> <p>13 Q. When in relation to</p> <p>14 January 15, 2019?</p> <p>15 A. Today is the --</p> <p>16 Q. Is the 21st.</p> <p>17 A. Today is the 21st. I would</p> <p>18 say somewhere between the 15th and the</p> <p>19 21st. Actually it was this past Saturday</p> <p>20 as it was placed in my Dropbox and I</p> <p>21 could not open my Dropbox.</p> <p>22 Q. When did you review Exhibit</p> <p>23 Number 3?</p> <p>24 A. That same report?</p>

<p style="text-align: right;">Page 38</p> <p>1 Q. Yes.</p> <p>2 A. I received it on Saturday.</p> <p>3 I reviewed it on Sunday.</p> <p>4 Q. How much time did you spend</p> <p>5 reviewing this additional Longo and</p> <p>6 Rigler report?</p> <p>7 A. Sorry. About three hours.</p> <p>8 Q. Did you read every page?</p> <p>9 A. I read -- I reviewed each</p> <p>10 page but I did not scrutinize every page.</p> <p>11 Q. Did you read the entirety of</p> <p>12 the text in this supplemental report?</p> <p>13 A. May I see the report,</p> <p>14 please.</p> <p>15 MS. O'DELL: Objection.</p> <p>16 Asked and answered. That's the</p> <p>17 same question.</p> <p>18 THE WITNESS: Should I</p> <p>19 answer?</p> <p>20 MS. O'DELL: Yes, you may.</p> <p>21 THE WITNESS: I reviewed the</p> <p>22 text going up to Page 32 with</p> <p>23 greater rigor than I did the</p> <p>24 tables.</p>	<p style="text-align: right;">Page 40</p> <p>1 A. The attorneys.</p> <p>2 Q. I'm going to show you --</p> <p>3 A. Plaintiffs' attorneys.</p> <p>4 (Document marked for</p> <p>5 identification as Exhibit</p> <p>6 Zelickoff-4.)</p> <p>7 BY MR. HEGARTY:</p> <p>8 Q. I'm going to show you what I</p> <p>9 marked as Exhibit Number 4. This is the</p> <p>10 MDL report provided to us for Michael</p> <p>11 Crowley.</p> <p>12 A. Mm-hmm.</p> <p>13 Q. Did you read the entirety of</p> <p>14 that report?</p> <p>15 A. I cannot say that I read the</p> <p>16 entirety of this report. I reviewed the</p> <p>17 report.</p> <p>18 Q. Okay. Well, your report is</p> <p>19 dated November 16, 2018. And that report</p> <p>20 is dated November 12, 2012, -- 2018.</p> <p>21 When did you receive the report by</p> <p>22 Dr. Crowley in relation to the date on</p> <p>23 the first page, November 12th.</p> <p>24 A. I really cannot say with</p>
<p style="text-align: right;">Page 39</p> <p>1 BY MR. HEGARTY:</p> <p>2 Q. When you say "reviewed,"</p> <p>3 does that mean that you read every -- all</p> <p>4 the words on every page up to Page 32?</p> <p>5 A. I did.</p> <p>6 Q. You included in the list of</p> <p>7 reports that you reviewed, the report of</p> <p>8 Michael Crowley, correct?</p> <p>9 A. Every one of the reports</p> <p>10 were not read with the -- read with</p> <p>11 the -- sorry, I'm caught up in the</p> <p>12 microphone -- were not read with the same</p> <p>13 intensity and duration of time put into</p> <p>14 it. I reviewed it. To what extent, I'm</p> <p>15 not clear at this moment.</p> <p>16 Q. The first report that you</p> <p>17 list in the list of reports in Exhibit B</p> <p>18 is the expert report of Michael M.</p> <p>19 Crowley, correct?</p> <p>20 A. It's written that way, yes.</p> <p>21 Q. Did you prepare this list of</p> <p>22 reports?</p> <p>23 A. I did not.</p> <p>24 Q. Who did?</p>	<p style="text-align: right;">Page 41</p> <p>1 certainty. It seems to me that I</p> <p>2 received this prior to my report</p> <p>3 conclusion.</p> <p>4 Q. There are 212 pages there.</p> <p>5 Again, did you read every word of every</p> <p>6 page?</p> <p>7 A. No, sir. Did I look at</p> <p>8 every word of every page? Yes.</p> <p>9 Q. No, my question is did you</p> <p>10 read every word of every page.</p> <p>11 A. My answer is --</p> <p>12 MS. O'DELL: She answered</p> <p>13 your question.</p> <p>14 THE WITNESS: -- I looked at</p> <p>15 every page.</p> <p>16 BY MR. HEGARTY:</p> <p>17 Q. Did you read all the</p> <p>18 references that he has in that report?</p> <p>19 A. I looked at the references.</p> <p>20 Q. Did you actually pull the</p> <p>21 references and read the citations that he</p> <p>22 refers to?</p> <p>23 A. No, sir. I did my own -- my</p> <p>24 own literature search in terms of</p>

<p style="text-align: right;">Page 42</p> <p>1 fragrance and chemicals within the 2 fragrances. And I did receive that as an 3 exhibit this morning. 4 Q. I'm sorry. What did you 5 say? 6 A. I said I did my own 7 literature search in terms of fragrances, 8 and I think you received a copy of that 9 this morning. In that report that I did, 10 that I prepared, I was assessing 11 carcinogenicity of each of the compounds. 12 Q. Going back to the Crowley 13 report, did you read all the tables in 14 that report? 15 A. I did not read. I reviewed. 16 Q. What is -- 17 A. I looked at them. 18 Q. Okay. What is the 19 difference between reading and reviewing 20 to you? 21 A. In my mind, reading is 22 in-depth assessment, and whereas 23 reviewing is looking over. Reading is 24 more intense.</p>	<p style="text-align: right;">Page 44</p> <p>1 Dr. Crowley's report. And with that I -- 2 I used the case number. I reviewed each 3 one of the chemicals in terms of their 4 potential carcinogenicity by, number one, 5 putting -- writing down the chemical, 6 looking to see if there were other 7 structures or chemicals -- or chemicals 8 that had similar names. 9 I reviewed through Google, 10 through PubMed and through Tox Lit and 11 IARC reports to see whether or not there 12 was a listing for them in terms of 13 carcinogenicity. And that is the result. 14 This is the result. 15 Q. When did you do all of that? 16 A. I did that post the 17 report -- 18 Q. When -- sorry. 19 A. -- as part of my preparation 20 for the deposition. 21 Q. When did you do it post 22 report in relation to today? 23 A. One to two weeks ago. 24 Q. Did you review -- strike</p>
<p style="text-align: right;">Page 43</p> <p>1 Q. You pointed to us -- pointed 2 to us -- strike that. 3 You pointed to the document 4 that was provided to us this morning, 5 which you say is -- what I think you said 6 reflects your own literature search with 7 regard to fragrances; is that correct? 8 A. Mine and a student. 9 Q. What student? 10 A. A graduate student in my 11 laboratory. 12 (Document marked for 13 identification as Exhibit 14 Zelikoff-5.) 15 BY MR. HEGARTY: 16 Q. I've marked as Exhibit 17 Number 5 the document that was produced 18 to us this morning. Can you tell me what 19 Exhibit Number 5 is. 20 A. Exhibit Number 5 is -- is a 21 list of the chemicals that -- part of 22 which, if not in its entirety, were taken 23 from the fragrances that were -- and the 24 chemicals that were listed in</p>	<p style="text-align: right;">Page 45</p> <p>1 that. 2 Did you read all the MSDSes 3 that you list in Exhibit Number 5? 4 A. I did not read all of the 5 MSDSes. But I did look at them. I 6 reviewed them to make sure they were 7 accurate. 8 Q. Did you -- did you look at 9 and review every MSDS listed in Exhibit 10 Number 5? 11 A. No, sir. 12 Q. I'm sorry? 13 A. No, sir. 14 Q. Approximately how many did 15 you look at in review? 16 A. I would say I looked at 17 perhaps half. Looked -- looked at, not 18 reviewed. 19 Q. But with regard to your 20 analysis of the fragrances that are 21 reportedly in Johnson's Baby Powder, you 22 did not do any of your own analysis as of 23 the time of your report, correct? 24 A. I --</p>

<p style="text-align: right;">Page 46</p> <p>1 MS. O'DELL: Objection to</p> <p>2 the form.</p> <p>3 THE WITNESS: I did no</p> <p>4 analysis except to gather the</p> <p>5 information that is out there by</p> <p>6 reputable organizations.</p> <p>7 BY MR. HEGARTY:</p> <p>8 Q. Well, did you gather that</p> <p>9 information before you completed your</p> <p>10 expert report?</p> <p>11 A. I did this after my expert</p> <p>12 report.</p> <p>13 Q. And my question was, before</p> <p>14 your expert report, did you do any of</p> <p>15 your own analysis of the fragrances that</p> <p>16 we -- are listed in Exhibit Number 5?</p> <p>17 MS. O'DELL: Objection to</p> <p>18 form.</p> <p>19 THE WITNESS: I'm not sure</p> <p>20 what you mean by analysis.</p> <p>21 BY MR. HEGARTY:</p> <p>22 Q. Well, did you do any of your</p> <p>23 own research, review of the literature,</p> <p>24 anything with regard to fragrances as of</p>	<p style="text-align: right;">Page 48</p> <p>1 THE WITNESS: I --</p> <p>2 post-report, I did my own search.</p> <p>3 BY MR. HEGARTY:</p> <p>4 Q. But my question was, before</p> <p>5 your report, with regard to Dr. Crowley's</p> <p>6 report, did you actually pull the</p> <p>7 literature references that he cites and</p> <p>8 read them yourself?</p> <p>9 A. No, sir.</p> <p>10 Q. You also make reference to</p> <p>11 reviewing Dr. Longo's report, MDL report,</p> <p>12 which is dated November 14, 2018. That's</p> <p>13 in the last page of Exhibit Number B. Do</p> <p>14 you see that?</p> <p>15 A. I -- I see that, yes.</p> <p>16 Q. Did you read every page of</p> <p>17 that report?</p> <p>18 A. No, sir, I did not. But I</p> <p>19 did read every page of the December 2018</p> <p>20 Longo mass supplement report.</p> <p>21 Q. Well, focusing on the</p> <p>22 November 14, 2018, report, that report is</p> <p>23 over 2,000 pages. Are you aware of that?</p> <p>24 A. Yes, sir.</p>
<p style="text-align: right;">Page 47</p> <p>1 the time of your signing of your expert</p> <p>2 report November 16, 2018?</p> <p>3 A. I very briefly looked up</p> <p>4 limonene and eugenol. And it wasn't in</p> <p>5 regards to this case. It was in regards</p> <p>6 to work that I do with electronic</p> <p>7 cigarettes. They are being used as</p> <p>8 flavorants.</p> <p>9 Q. Was that the extent of your</p> <p>10 review of the fragrances as of the time</p> <p>11 of your expert report, November 16, 2018?</p> <p>12 MS. O'DELL: Object to form.</p> <p>13 You may answer.</p> <p>14 THE WITNESS: Whatever is in</p> <p>15 the report from Dr. Crowley that</p> <p>16 listed, I looked at those.</p> <p>17 BY MR. HEGARTY:</p> <p>18 Q. But as you indicated, you</p> <p>19 did not read all the citations, the</p> <p>20 literature resources that Dr. Crowley</p> <p>21 cites in his report and review them</p> <p>22 yourself?</p> <p>23 MS. O'DELL: Object to the</p> <p>24 form.</p>	<p style="text-align: right;">Page 49</p> <p>1 Q. Did you read all 2,000</p> <p>2 pages?</p> <p>3 A. No, sir. I did not.</p> <p>4 Q. Did you read any of those</p> <p>5 2,000 pages?</p> <p>6 A. I reviewed several of those</p> <p>7 pages.</p> <p>8 Q. Okay. How about the rest of</p> <p>9 the reports that are listed there? Did</p> <p>10 you read every page of the reports that</p> <p>11 are listed there?</p> <p>12 A. I read every page of the</p> <p>13 Dr. Thomas Dydek's report. And I read</p> <p>14 two-thirds of Dr. Plunkett's.</p> <p>15 Q. As to the rest, did you</p> <p>16 review the remaining reports?</p> <p>17 MS. O'DELL: Object to the</p> <p>18 form.</p> <p>19 BY MR. HEGARTY:</p> <p>20 Q. Or not look at them at all?</p> <p>21 A. I glanced over them.</p> <p>22 Q. Do you recall if you were</p> <p>23 ever provided any draft reports from any</p> <p>24 of the plaintiffs' experts in the MDL,</p>

<p style="text-align: right;">Page 50</p> <p>1 where you understood them to be drafts?</p> <p>2 A. I never received anything</p> <p>3 that I understood to be a draft document.</p> <p>4 (Document marked for</p> <p>5 identification as Exhibit</p> <p>6 Zelikoff-6.)</p> <p>7 BY MR. HEGARTY:</p> <p>8 Q. Dr. Zelikoff, I'm marking</p> <p>9 Exhibit Number 6 a copy of your</p> <p>10 deposition notice for purposes of today's</p> <p>11 deposition.</p> <p>12 A. Yes, sir. I see it.</p> <p>13 Q. Did you have a chance to</p> <p>14 look at that before today?</p> <p>15 A. I did not.</p> <p>16 Q. What materials did you bring</p> <p>17 with you to the deposition today?</p> <p>18 MS. O'DELL: I would just</p> <p>19 reassert that the objections that</p> <p>20 plaintiffs have served regarding</p> <p>21 certain of the requests and would</p> <p>22 state that Dr. Zelikoff has</p> <p>23 brought binders of her cited</p> <p>24 materials, and then I believe I</p>	<p style="text-align: right;">Page 52</p> <p>1 Q. Is it correct that the</p> <p>2 binders to your right are copies of</p> <p>3 everything in -- under the listing --</p> <p>4 under the heading of Materials and Data</p> <p>5 Considered?</p> <p>6 MS. O'DELL: Object to the</p> <p>7 form.</p> <p>8 THE WITNESS: I cannot say</p> <p>9 that every single paper in here is</p> <p>10 in there. Maybe in something that</p> <p>11 I have looked up, but I can't say</p> <p>12 with likely certainty that yes,</p> <p>13 everything is in there. Although</p> <p>14 I cannot tell you that I reviewed</p> <p>15 every single one and matched it to</p> <p>16 this page.</p> <p>17 BY MR. HEGARTY:</p> <p>18 Q. Who prepared -- who prepared</p> <p>19 the document Materials and Data</p> <p>20 Considered?</p> <p>21 A. What do you mean by</p> <p>22 prepared?</p> <p>23 Q. Did you prepare it?</p> <p>24 MS. O'DELL: Object to the</p>
<p style="text-align: right;">Page 51</p> <p>1 gave you a jump drive of all the</p> <p>2 reference materials.</p> <p>3 BY MR. HEGARTY:</p> <p>4 Q. Let me go back to my</p> <p>5 question. Sitting to your right are</p> <p>6 binders of materials. Do you know what</p> <p>7 those binders are, Dr. Zelikoff?</p> <p>8 A. I do know what those black</p> <p>9 binders are to my right.</p> <p>10 Q. What are they?</p> <p>11 A. They are binders containing</p> <p>12 materials, papers, literature --</p> <p>13 literature, in alphabetical order of</p> <p>14 papers that are relevant to my -- to my</p> <p>15 testimony, as well as production</p> <p>16 documents which include letters, reports</p> <p>17 of internal documents.</p> <p>18 Q. Your Exhibit B in your</p> <p>19 report starts with a page Materials and</p> <p>20 Data Considered. Do you see that?</p> <p>21 A. Page please?</p> <p>22 Q. It's Exhibit B.</p> <p>23 A. Materials and data</p> <p>24 considered, I have it, yes, sir.</p>	<p style="text-align: right;">Page 53</p> <p>1 form.</p> <p>2 THE WITNESS: I supplied</p> <p>3 data, references, and in</p> <p>4 coordination and complementation</p> <p>5 with the plaintiffs' attorneys,</p> <p>6 they prepared this.</p> <p>7 (Document marked for</p> <p>8 identification as Exhibit</p> <p>9 Zelikoff-7.)</p> <p>10 BY MR. HEGARTY:</p> <p>11 Q. I'm marking as Exhibit</p> <p>12 Number 7 a flash drive that we were</p> <p>13 provided here today. Do you know what</p> <p>14 Exhibit Number 7 is?</p> <p>15 A. I do not.</p> <p>16 Q. Do you know what's contained</p> <p>17 on the flash drive?</p> <p>18 A. I have not seen the data</p> <p>19 within the flash drive.</p> <p>20 MS. O'DELL: I'll just</p> <p>21 represent that I prepared the</p> <p>22 flash drive and the flash drive</p> <p>23 has all the materials on</p> <p>24 Exhibit B, on behalf of</p>

<p style="text-align: right;">Page 54</p> <p>1 Dr. Zelikoff.</p> <p>2 BY MR. HEGARTY:</p> <p>3 Q. Are the materials you also</p> <p>4 cited -- I'm sorry. Are the references</p> <p>5 you also cited in the body of your report</p> <p>6 contained in those notebooks to your</p> <p>7 knowledge?</p> <p>8 A. To my knowledge, they are.</p> <p>9 Q. Are the materials that --</p> <p>10 that are in those notebooks materials you</p> <p>11 reviewed or had access to prior to</p> <p>12 completion of your expert report?</p> <p>13 A. Prior to the completion.</p> <p>14 However I also prepared my own. So in</p> <p>15 going through -- in coming to my</p> <p>16 conclusion and opinion, I also went</p> <p>17 through the literature using various</p> <p>18 websites including, as I said Tox Lit,</p> <p>19 Google and PubMed. And I arranged my</p> <p>20 documents that I thought were relevant</p> <p>21 after reviewing all of the ones that came</p> <p>22 up in my literature search, and I</p> <p>23 reviewed the abstracts and if I found</p> <p>24 them to be relevant, I placed them in --</p>	<p style="text-align: right;">Page 56</p> <p>1 Q. You had not read that</p> <p>2 manuscript though at the time you</p> <p>3 completed your report, correct?</p> <p>4 A. No, I did not, sir.</p> <p>5 Q. So that manuscript did not</p> <p>6 inform the opinions set out in your</p> <p>7 report, correct?</p> <p>8 MS. O'DELL: Objection to</p> <p>9 form.</p> <p>10 THE WITNESS: Do I answer?</p> <p>11 MS. O'DELL: Yes, you may</p> <p>12 answer.</p> <p>13 THE WITNESS: Okay.</p> <p>14 MS. O'DELL: Yes.</p> <p>15 THE WITNESS: I -- I had</p> <p>16 access to an abstract from the</p> <p>17 same author with emerging results</p> <p>18 that was brought forward in larger</p> <p>19 context and in greater detail in</p> <p>20 the publication. So I had -- so</p> <p>21 the abstract did go into my</p> <p>22 thinking.</p> <p>23 BY MR. HEGARTY:</p> <p>24 Q. The manuscript though we</p>
<p style="text-align: right;">Page 55</p> <p>1 in order and in bins, in silos, in</p> <p>2 different areas, and I prepared my own.</p> <p>3 Q. We were also provided today,</p> <p>4 this morning, what I've marked as Exhibit</p> <p>5 Number 8 which is a manuscript from a</p> <p>6 publication called Reproductive Sciences.</p> <p>7 The lead author, Ghassam Saed.</p> <p>8 (Document marked for</p> <p>9 identification as Exhibit</p> <p>10 Zelikoff-8.)</p> <p>11 BY MR. HEGARTY:</p> <p>12 Q. Can you tell me when you</p> <p>13 received that manuscript?</p> <p>14 A. I received the manuscript in</p> <p>15 December.</p> <p>16 Q. Approximately when in</p> <p>17 December?</p> <p>18 A. Let me say that it was</p> <p>19 either December or early January. I</p> <p>20 cannot be more exact than that.</p> <p>21 Q. Have you read that</p> <p>22 manuscript?</p> <p>23 A. Have I -- yes, I've read</p> <p>24 this manuscript.</p>	<p style="text-align: right;">Page 57</p> <p>1 marked as Exhibit 8 did not go into your</p> <p>2 thinking?</p> <p>3 A. The manuscript -- no, sir,</p> <p>4 it did not. It did post my report and it</p> <p>5 added supplementary and compelling</p> <p>6 evidence for my opinion.</p> <p>7 (Document marked for</p> <p>8 identification as Exhibit</p> <p>9 Zelikoff-9.)</p> <p>10 BY MR. HEGARTY:</p> <p>11 Q. I've also marked as Exhibit</p> <p>12 Number 9 another document we were</p> <p>13 provided this morning which is -- which</p> <p>14 is called Draft Screening Assessment.</p> <p>15 When did you receive this</p> <p>16 draft screening assessment?</p> <p>17 A. January.</p> <p>18 Q. Approximately when in</p> <p>19 January?</p> <p>20 A. About two weeks ago.</p> <p>21 Q. Who -- what was your source</p> <p>22 for getting that document?</p> <p>23 A. Ms. Emmel.</p> <p>24 Q. Did Ms. Emmel also provide</p>

<p style="text-align: right;">Page 58</p> <p>1 the -- the Saed manuscript?</p> <p>2 A. Yes, sir, she did.</p> <p>3 Q. So neither the Canadian</p> <p>4 assessment nor Dr. Saed's manuscript were</p> <p>5 materials you found on your own, correct?</p> <p>6 A. Correct.</p> <p>7 Q. Do you know how Ms. Emmel</p> <p>8 came to receive an unpublished</p> <p>9 manuscript, apart from any discussions</p> <p>10 that you had with plaintiffs' counsel?</p> <p>11 A. Actually, which manuscript</p> <p>12 are you referring to?</p> <p>13 Q. Well, there's only one</p> <p>14 manuscript in front of you?</p> <p>15 A. Reproductive Science --</p> <p>16 Q. Dr. -- yes.</p> <p>17 A. -- Dr. Saed?</p> <p>18 To my knowledge, this has --</p> <p>19 and seeing the cover letter that was</p> <p>20 associated with this, this is not a</p> <p>21 manuscript. This is an in-press</p> <p>22 manuscript, and there is a very large</p> <p>23 difference.</p> <p>24 Q. Okay. Apart from anything</p>	<p style="text-align: right;">Page 60</p> <p>1 that is a supplement of that or a -- an</p> <p>2 adjacent document.</p> <p>3 Q. Do you have that document</p> <p>4 with you?</p> <p>5 A. Perhaps. I do, yes, sir.</p> <p>6 Q. May I see it, please.</p> <p>7 (Document marked for</p> <p>8 identification as Exhibit</p> <p>9 Zelickoff-10.)</p> <p>10 BY MR. HEGARTY:</p> <p>11 Q. I'm going to mark as Exhibit</p> <p>12 Number 10 what you just handed to me,</p> <p>13 which is titled "Systematic Review and</p> <p>14 Meta-Analysis of the Association Between</p> <p>15 Perineal Use of Talc and Risk of Ovarian</p> <p>16 Cancer," lead author Taher.</p> <p>17 When did you receive Exhibit</p> <p>18 Number 10?</p> <p>19 MS. O'DELL: Did we skip</p> <p>20 nine?</p> <p>21 MR. HEGARTY: Exhibit 9 is</p> <p>22 the draft screening assessment.</p> <p>23 MS. O'DELL: Okay. I'm</p> <p>24 sorry. I had that as Number 8.</p>
<p style="text-align: right;">Page 59</p> <p>1 that counsel for plaintiffs may have told</p> <p>2 you, do you know how this manuscript</p> <p>3 became available for you to review?</p> <p>4 A. I have no knowledge.</p> <p>5 Q. With regard to the</p> <p>6 Canadian -- sorry, the draft screening</p> <p>7 assessment, did you read the entirety of</p> <p>8 this assessment?</p> <p>9 A. I'm looking for it right</p> <p>10 now.</p> <p>11 Q. Sorry.</p> <p>12 A. Thank you. Except for the</p> <p>13 references, I read the entirety of the</p> <p>14 text.</p> <p>15 Q. Did you pull the references</p> <p>16 and review the references themselves?</p> <p>17 A. No, sir, I did not.</p> <p>18 Q. There are also supplemental</p> <p>19 materials associated with this -- or do</p> <p>20 you know whether there are supplemental</p> <p>21 materials associated with this draft, or</p> <p>22 with this draft screening assessment?</p> <p>23 A. I was also provided a</p> <p>24 document by Dr. Taher. I'm not sure if</p>	<p style="text-align: right;">Page 61</p> <p>1 MR. HEGARTY: Number 8 is</p> <p>2 the manuscript by Dr. Saed.</p> <p>3 MS. O'DELL: Okay. I'm</p> <p>4 sorry.</p> <p>5 BY MR. HEGARTY:</p> <p>6 Q. Going back to my question,</p> <p>7 when did you receive the article by</p> <p>8 Taher?</p> <p>9 A. At the same time that I</p> <p>10 received the health -- the screening</p> <p>11 health assessment from Health Canada.</p> <p>12 Q. Who provided it to you?</p> <p>13 A. Ms. Emmel.</p> <p>14 Q. Did you read the entirety of</p> <p>15 that document?</p> <p>16 A. I read the entirety of this</p> <p>17 document minus the references.</p> <p>18 Q. Did you pull the literature</p> <p>19 cited in the Taher article and review it</p> <p>20 yourself?</p> <p>21 A. I may have looked at</p> <p>22 references that have -- were on the</p> <p>23 reference list of the Saed document, but</p> <p>24 I did not go through each individual</p>

<p style="text-align: right;">Page 62</p> <p>1 reference in the document and pull it</p> <p>2 specifically.</p> <p>3 Q. The Taher article -- strike</p> <p>4 that.</p> <p>5 You were provided the Taher</p> <p>6 article after you completed your expert</p> <p>7 report in this case, correct?</p> <p>8 A. That's correct.</p> <p>9 Q. So it's correct that it did</p> <p>10 not inform your opinions in your report,</p> <p>11 correct?</p> <p>12 A. It informed my opinions --</p> <p>13 let me say that it added to my opinions</p> <p>14 following the writing of my report. It</p> <p>15 supported my position.</p> <p>16 Q. Did the assessment conclude</p> <p>17 that talc use causes ovarian cancer?</p> <p>18 Strike that. Let me strike that</p> <p>19 question. We'll come back to that.</p> <p>20 (Document marked for</p> <p>21 identification as Exhibit</p> <p>22 Zelikoff-11.)</p> <p>23 BY MR. HEGARTY:</p> <p>24 Q. I'm going to mark next as</p>	<p style="text-align: right;">Page 64</p> <p>1 Q. Have you reviewed any</p> <p>2 materials since completion of your report</p> <p>3 for purposes of your work on this case</p> <p>4 that we have not talked about this</p> <p>5 morning?</p> <p>6 A. I reviewed -- since my</p> <p>7 report, I reviewed Dr. Pier's deposition.</p> <p>8 Is that what you mean?</p> <p>9 Q. Dr. Julie Pier's deposition?</p> <p>10 A. Yes. Three-quarters of it.</p> <p>11 It is a very long deposition.</p> <p>12 Q. The second-to-last page of</p> <p>13 Exhibit Number B under depositions makes</p> <p>14 reference to depositions and exhibits of</p> <p>15 Julie Pier dated 9/12 to 9/13/2018.</p> <p>16 Do you see that?</p> <p>17 A. Sorry, sir. Fifth line</p> <p>18 down, deposition/exhibits of Julie Pier.</p> <p>19 Q. Is that the deposition to</p> <p>20 which you just referred?</p> <p>21 A. To the best of my knowledge.</p> <p>22 Q. Anything else that you have</p> <p>23 reviewed for purposes of your work on</p> <p>24 this case that we have not talked about</p>
<p style="text-align: right;">Page 63</p> <p>1 Exhibit Number 11 a copy of the Exhibit C</p> <p>2 that's referenced in your report.</p> <p>3 Did you prepare Exhibit</p> <p>4 Number C?</p> <p>5 A. If you mean by preparation,</p> <p>6 did I write it, did I prepare the</p> <p>7 summary, no, sir I did not.</p> <p>8 Q. Do you know who prepared it?</p> <p>9 A. From my reading, it appears</p> <p>10 as though the attorneys may have prepared</p> <p>11 it based upon -- to my knowledge, based</p> <p>12 upon other deponents.</p> <p>13 Q. Other than the documents</p> <p>14 that we have talked about that are laid</p> <p>15 out before us, did you bring any other</p> <p>16 documents with you to the deposition?</p> <p>17 A. Other than the documents</p> <p>18 that are to my right in the folders, the</p> <p>19 health assessment from the -- the</p> <p>20 screening health assessment from Canada,</p> <p>21 Dr. Taher's paper, a letter -- this is in</p> <p>22 the documents to my right, a letter from</p> <p>23 Luzenac to Dr. Al Wehner, my CV, the</p> <p>24 expert report, Exhibit B, my CV, no, sir.</p>	<p style="text-align: right;">Page 65</p> <p>1 this morning or made reference to?</p> <p>2 A. I reviewed Dr. Hopkins'</p> <p>3 report.</p> <p>4 Q. Let me ask it different.</p> <p>5 Anything that you have reviewed that's</p> <p>6 either not listed somewhere in your</p> <p>7 report or we have not marked as an</p> <p>8 exhibit?</p> <p>9 A. To the best of my knowledge,</p> <p>10 no.</p> <p>11 Q. With regard to Exhibit C,</p> <p>12 did you review all the documents that are</p> <p>13 referenced in Exhibit Number C?</p> <p>14 A. Can I see that, please.</p> <p>15 Q. I think you still have a</p> <p>16 copy in front of you.</p> <p>17 A. Okay.</p> <p>18 Q. It's Exhibit Number 11,</p> <p>19 which is marked Exhibit -- which is</p> <p>20 Exhibit C. Did you actually pull the</p> <p>21 documents and confirm the accuracy of the</p> <p>22 information --</p> <p>23 A. No, sir.</p> <p>24 Q. -- contained in Exhibit C?</p>

<p style="text-align: right;">Page 66</p> <p>1 A. There are no -- there are no 2 references in here, as I understand it. 3 Q. Well, there are Bates 4 numbers -- 5 A. Bates numbers. 6 Q. -- that are listed at the 7 right, which correspond to documents, 8 correct? 9 A. Yes, but when I -- when I 10 hear references I think of citations, 11 papers. 12 Q. Did you actually pull the 13 documents whose Bates numbers are listed 14 and confirm the accuracy of the 15 information contained in Exhibit C? 16 A. I did not pull them as part 17 of reviewing this exhibit, but I have 18 looked at them, because I have gone 19 through all of the production documents. 20 Q. With regard to your expert 21 report in this case, is it correct that 22 you prepared that report -- strike that. 23 With regard to your expert 24 report it defines the scope of your</p>	<p style="text-align: right;">Page 68</p> <p>1 BY MR. HEGARTY: 2 Q. You agree that the standard 3 for proving biologic plausibility or any 4 other scientific issue in the medical 5 literature is the same one that applies 6 in litigation, correct? 7 MS. O'DELL: Object to the 8 form. If you know. 9 THE WITNESS: Can you repeat 10 that, please. 11 BY MR. HEGARTY: 12 Q. Sure. You agree that the 13 standard for proving biologic 14 plausibility or any other scientific 15 issue in a medical literature or in 16 science should be the same that is 17 applied in litigation? 18 MS. O'DELL: Object to the 19 form. 20 THE WITNESS: I will use the 21 same scrutiny and rigor, as I said 22 before. 23 BY MR. HEGARTY: 24 Q. You would -- you intend to</p>
<p style="text-align: right;">Page 67</p> <p>1 testimony in this case, correct? 2 MS. O'DELL: Objection to 3 form. 4 THE WITNESS: Yes, it does. 5 BY MR. HEGARTY: 6 Q. And is it correct that the 7 report was prepared with the same 8 methodology and approach as you would 9 have prepared an article for publication 10 in a scientific journal? 11 A. An article, a grant, a 12 review, an advisory board report, with 13 the same rigor and the same scrutiny, 14 yes. 15 Q. In other words, is it 16 correct that you prepared this report in 17 the same manner as you had prepared all 18 of your articles for publication? 19 MS. O'DELL: Asked and 20 answered. 21 THE WITNESS: I used the 22 same methodology, the same 23 scrutiny and the same rigor to 24 prepare this, yes.</p>	<p style="text-align: right;">Page 69</p> <p>1 apply the same standards to your report 2 and your opinions in this case as you 3 would apply if you were looking at this 4 as simply a professor at New York 5 University? 6 A. Well, I don't see simply a 7 professor. 8 If I were -- I review 9 papers. I think I've answered this 10 already. But I review papers and 11 literature with the same scrutiny as I 12 prepared this report. 13 Q. Did you apply the same 14 standard for assessing biologic 15 plausibility as you apply in your work at 16 NY University? 17 A. I do. 18 Q. Did you sign your report 19 dated November 16, 2018, with the same 20 intent as if signed under penalty of 21 perjury? 22 A. Could you repeat that 23 please. 24 Q. Sure. Did you sign your</p>

<p style="text-align: right;">Page 70</p> <p>1 expert report dated November 16, 2018, 2 with the same intent as if signed under 3 penalty of perjury? 4 MS. O'DELL: Object to form. 5 THE WITNESS: I'm not sure I 6 understand what that question 7 means. 8 BY MR. HEGARTY: 9 Q. Well, did you -- by signing 10 this report, did you confirm to the 11 accuracy of everything contained in the 12 report? 13 A. To the best of my knowledge, 14 I signed this report knowing that I 15 prepared this report and there is -- with 16 the same intent of accuracy and rigor. 17 Q. You understand this is 18 supposed to be your testimony as if on a 19 stand before a judge or a jury, correct? 20 MS. O'DELL: Object to the 21 form. 22 THE WITNESS: My 23 understanding of the deposition is 24 that it is a legal document and</p>	<p style="text-align: right;">Page 72</p> <p>1 that these are my -- my report 2 reflects my opinion. 3 BY MR. HEGARTY: 4 Q. Are they -- are there any 5 necessary changes, or revisions to your 6 report? 7 A. Not to my knowledge. 8 Q. And all the opinions that 9 you intend to offer in this litigation 10 are set out in your report, as you just 11 said, correct? 12 A. To come to my decision or my 13 opinion, prior to -- included all the 14 documents that I had in my possession and 15 were -- had access to prior to my report. 16 Q. My question is a little bit 17 different, Doctor. My question is, the 18 opinions that you intend to offer as you 19 just indicated, those are set out in your 20 report, correct? 21 A. The opinions that I intend 22 to offer, yes. 23 Q. As your report shows, you 24 don't intend to offer the opinion that</p>
<p style="text-align: right;">Page 71</p> <p>1 testifying my -- my opinion. And 2 that it has to be honest and 3 truthful and transparent. 4 BY MR. HEGARTY: 5 Q. Well, this time I'm talking 6 about your report. Do you understand 7 your report is supposed to be your 8 testimony as if you are before a judge 9 and a jury? 10 MS. O'DELL: Object to the 11 form. 12 THE WITNESS: I -- I 13 understand that this has to be 14 honest and truthful, and this will 15 be -- could be, will be, the basis 16 for my testimony in a court trial, 17 if that is what you're asking. 18 BY MR. HEGARTY: 19 Q. You understand it's supposed 20 to set out your -- the entirety of your 21 opinions in this case? 22 MS. O'DELL: Object to the 23 form. 24 THE WITNESS: I understand</p>	<p style="text-align: right;">Page 73</p> <p>1 use of Johnson's Baby Powder or Shower to 2 Shower causes ovarian cancer, correct? 3 A. My mission, the question 4 that I was asked by plaintiff attorney 5 was to confer or to assess biological 6 plausibility in the causation of talc for 7 ovarian cancer. 8 Q. And as your report shows, 9 you did not do a risk assessment or 10 Bradford Hill analysis of all the 11 literature looking at talc products and 12 ovarian cancer, correct? 13 A. I think I answered that, but 14 I'm not an epidemiologist, and my -- my 15 question was to look at biological 16 plausibility. 17 Q. And all the materials that 18 you intend to rely upon for purposes of 19 your opinions, are those set out in your 20 report, those we've talked about here 21 this morning, correct? 22 A. Yes, including the 23 contributions that were made after my 24 report including Dr. Longo's supplement,</p>

<p style="text-align: right;">Page 74</p> <p>1 including Dr. Saed's paper. They added 2 to my opinion, supplemented them. But it 3 is -- but my -- my opinion stays the same 4 as the report. 5 Q. Okay. 6 MR. HEGARTY: The next 7 section I have is pretty long. I 8 don't know if you want to take a 9 quick break now or just keep 10 going. It's up to you. 11 MS. O'DELL: We've been 12 going about an hour. I think 13 that's probably a good idea. 14 MR. HEGARTY: Because 15 otherwise it's not -- there's not 16 going to be a good break time. So 17 we should probably do it now. 18 MS. O'DELL: Well, we can 19 definitely do it now, but we'll -- 20 of course we'll break when the 21 witness needs to break. 22 MR. HEGARTY: Understood. 23 Understood. But you know what I 24 mean.</p>	<p style="text-align: right;">Page 76</p> <p>1 by more than one investigator, and is a 2 compilation of different points, then 3 I -- I will use -- I will not necessarily 4 put quotations around it. And I will not 5 necessarily reference it, because it's -- 6 may have been taken from another document 7 but it's common knowledge. 8 Q. What about -- 9 A. And it's -- 10 Q. I'm sorry. I didn't mean to 11 interrupt. 12 A. I couldn't -- I'm sorry. I 13 couldn't write it any better than as it 14 was put. 15 Q. What about if you take 16 materials from a published article for 17 purposes of your report, did you 18 reference those articles? 19 A. In some cases, not. Again, 20 it's my opinion that if there is 21 something that is stated by an 22 investigator and it's written extremely 23 well, and it's common knowledge for 24 scientists in that area, as well as</p>
<p style="text-align: right;">Page 75</p> <p>1 MS. O'DELL: Yeah. 2 THE VIDEOGRAPHER: Stand by 3 please. The time is 10:11 a.m. 4 Off the record. 5 (Short break.) 6 THE VIDEOGRAPHER: We are 7 back on the record. The time is 8 10:26 a.m. 9 BY MR. HEGARTY: 10 Q. Dr. Zelickoff, with regard to 11 your expert report, do you have that in 12 front of you? 13 A. I do now. Thank you. 14 Q. We marked that as exhibit 15 what? 16 A. Exhibit 2. 17 Q. With regard to Exhibit 18 Number 2, is it your testimony that all 19 of the sentences in your report are your 20 own words and not copied from others, 21 except where you used quotations? 22 A. Mm-hmm. The way I report 23 and write publications is if something 24 is, I feel, common knowledge or provided</p>	<p style="text-align: right;">Page 77</p> <p>1 others, then I will -- I will use it. 2 Q. That's not how you prepare 3 your report -- that's not how you prepare 4 your articles for journals though, 5 correct? 6 A. No, that's the same way I 7 prepare them. 8 If they are -- if they are, 9 again, common knowledge, I will not 10 necessarily cite them. 11 Q. Is it not your approach that 12 authors are to cite material to which 13 they are relying on or referring to in 14 published articles? 15 A. Again, I think you're asking 16 me the same question. But again, if 17 something is well known, then I do not 18 necessarily reference it. 19 Q. What is the definition -- 20 what is your definition of well known? 21 A. For example, if chromium -- 22 let's use nickel instead. If nickel is 23 being spoken about by IARC, by U.S. EPA, 24 by National Toxicology Program, and</p>

<p style="text-align: right;">Page 78</p> <p>1 they're all saying the same thing, I in 2 some cases may take what the IARC has 3 said and put it in my reference. 4 Q. And it's your testimony that 5 you do that in all -- you've done that in 6 all the articles that you've ever 7 published? 8 MS. O'DELL: Objection to 9 form. 10 THE WITNESS: I can't say 11 about all the articles. I 12 published over 130 -- 13 MR. HEGARTY: Mark -- 14 THE WITNESS: -- 15 publications and book chapters. 16 (Document marked for 17 identification as Exhibit 18 Zelikoff-12.) 19 BY MR. HEGARTY: 20 Q. Let me mark as Exhibit 21 Number 12 the academic integrity for 22 students at NYU policy. Is this the 23 policy applicable to your university? 24 A. It appears to be that you've</p>	<p style="text-align: right;">Page 80</p> <p>1 Q. Is that not -- is that a 2 definition you agree with? 3 A. I agree that there's ways to 4 interpret that. 5 Q. Is that -- is that the 6 definition New York University applies to 7 its students? 8 A. This sentence, "Presenting 9 others' work without adequate 10 acknowledgment of its source as though it 11 were one's own," that is for students. 12 That is not what I'm doing in my opinion. 13 In my opinion, I'm taking 14 common knowledge and presenting it. 15 Q. Well, they go on to give 16 examples of plagiarism that include, "A 17 sequence of words incorporated without 18 quotation marks." 19 Do you see where I'm 20 reading? 21 A. I do see it. "A sequence of 22 words incorporated without quotation 23 marks." 24 Q. It also says that,</p>
<p style="text-align: right;">Page 79</p> <p>1 taken it off the website in the academic 2 integrity for students at NYU. 3 Q. If you turn to the second 4 page, there is a definition of 5 plagiarism, that says, "Presenting 6 others' works without adequate 7 acknowledgment of its source as though it 8 were one's own." 9 A. I'm sorry. 10 Q. Do you agree with that 11 definition? 12 A. I'm sorry. What -- 13 Q. Second page of Exhibit 12. 14 A. You mean on the back? Is it 15 under Number 2, Number 1? 16 Q. Number 1. The definition of 17 plagiarism by your university for your 18 students is, "Presenting others' work 19 without adequate acknowledgement of its 20 source as though it were one's own." 21 Do you agree with that -- 22 that definition? 23 A. I agree that there's many 24 different ways to interpret that.</p>	<p style="text-align: right;">Page 81</p> <p>1 "Plagiarism is an unacknowledged passage 2 paraphrased from another's work." 3 Do you see that? 4 A. Some examples of plagiarism, 5 "Unacknowledged passage rephrased from 6 another's work." 7 Q. Do you agree those are -- 8 the two definitions that I just read from 9 your university's own policy for students 10 are examples of plagiarism? 11 A. This is the NYU 12 interpretation or what they've put on the 13 website, yes. 14 Q. Should this be a policy -- 15 strike that. 16 Is this a policy that 17 applies to students at NY university? 18 A. It applies -- it's an 19 academic integrity for students at NYU. 20 Q. Do you agree that professors 21 at NY university should also conform to 22 this policy? 23 A. I believe that honesty, 24 transparency is the key factor for all</p>

<p style="text-align: right;">Page 82</p> <p>1 scientists at any level.</p> <p>2 Q. You would agree that this</p> <p>3 should apply to your work as well,</p> <p>4 correct?</p> <p>5 A. I think that this definition</p> <p>6 is open to interpretation.</p> <p>7 Q. Well, do you either agree or</p> <p>8 disagree that this -- well, strike that.</p> <p>9 Do you agree that this</p> <p>10 policy should be applied to your work in</p> <p>11 this case?</p> <p>12 A. I agree that plagiarism is</p> <p>13 defined as presenting others' work</p> <p>14 without adequate acknowledgment of its</p> <p>15 source as though it were one's own.</p> <p>16 That's the NYU policy for students.</p> <p>17 Q. Did you -- you did that in</p> <p>18 your own report, correct?</p> <p>19 MS. O'DELL: Object to form.</p> <p>20 THE WITNESS: I did what in</p> <p>21 my own report?</p> <p>22 BY MR. HEGARTY:</p> <p>23 Q. You plagiarized portions of</p> <p>24 other people's work without proper</p>	<p style="text-align: right;">Page 84</p> <p>1 Q. Do you know who Shawn Levy</p> <p>2 is?</p> <p>3 A. I do not.</p> <p>4 Q. Did you review Dr. Levy's</p> <p>5 report for purposes of your -- preparing</p> <p>6 your report in this case?</p> <p>7 A. I actually looked at it, but</p> <p>8 did not -- did not read it.</p> <p>9 Q. When did you have a chance</p> <p>10 to look at his expert report?</p> <p>11 A. I have looked at it -- I'm</p> <p>12 trying to gather the knowledge. I</p> <p>13 actually do not recall when I looked at</p> <p>14 it.</p> <p>15 Q. If you look at your report</p> <p>16 on Page 20. In that exhibit, Doctor.</p> <p>17 A. Oh okay.</p> <p>18 Q. Your report and the portion</p> <p>19 of Dr. Levy's report is attached, and if</p> <p>20 you look at your report Page 20 and his</p> <p>21 report Page 5 --</p> <p>22 MS. O'DELL: I think, Mark,</p> <p>23 I think there's confusion because</p> <p>24 there's two documents put together</p>
<p style="text-align: right;">Page 83</p> <p>1 acknowledgment, correct?</p> <p>2 MS. O'DELL: Objection to</p> <p>3 form.</p> <p>4 THE WITNESS: That is</p> <p>5 totally incorrect.</p> <p>6 I used sentences from other</p> <p>7 people's -- other people's papers</p> <p>8 because they were common knowledge</p> <p>9 and contributed by multiple</p> <p>10 authors. And it was --</p> <p>11 BY MR. HEGARTY:</p> <p>12 Q. I'm going to mark -- sorry.</p> <p>13 A. And it was stated in a way</p> <p>14 that I couldn't have stated better.</p> <p>15 Q. I'm going to mark as</p> <p>16 Exhibit 13 a report -- a portion of your</p> <p>17 report dated November 16, 2018. And the</p> <p>18 back of that is a portion of Rule 26</p> <p>19 expert report of an expert by the name of</p> <p>20 Shawn Levy.</p> <p>21 (Document marked for</p> <p>22 identification as Exhibit</p> <p>23 Zelickoff-13.)</p> <p>24 BY MR. HEGARTY:</p>	<p style="text-align: right;">Page 85</p> <p>1 in this --</p> <p>2 MR. HEGARTY: Right. One is</p> <p>3 her report and one is Levy's</p> <p>4 report.</p> <p>5 MS. O'DELL: I just think</p> <p>6 that that was the confusion.</p> <p>7 THE WITNESS: Thank you.</p> <p>8 BY MR. HEGARTY:</p> <p>9 Q. So the -- do you see that</p> <p>10 sentences marked as 1 and 2 from</p> <p>11 Dr. Levy's report are identical to</p> <p>12 sentences marked 1 and 2 in your report?</p> <p>13 MS. O'DELL: Object to form.</p> <p>14 And, Doctor, if you need to</p> <p>15 take the documents apart and</p> <p>16 compare them, rather than flipping</p> <p>17 back and forth, if that would be</p> <p>18 helpful to you, feel free to do</p> <p>19 that.</p> <p>20 THE WITNESS: Good idea. I</p> <p>21 actually don't recall. Could</p> <p>22 you -- could you tell me when my</p> <p>23 report is dated please?</p> <p>24 BY MR. HEGARTY:</p>

<p style="text-align: right;">Page 86</p> <p>1 Q. November 16. His report is 2 also dated November 16. 3 A. I did not actually see this 4 report until after mine. 5 However, let me address your 6 question to the best of my ability. 7 "Things stated as both 8 inherited and acquired gene mutations 9 work together to cause cancer." 10 Everyone from the time of 11 their scientific career back in college 12 knows that. 13 "While genetic testing" -- 14 let me make sure I have both -- "both 15 inherited and acquired gene mutations 16 work together to cause cancer." 17 How -- there is no way for 18 me to say that differently. This is a 19 very well statement, very well put 20 statement. I used it without a 21 reference. Even if one -- 22 Q. My question -- I'm sorry. I 23 thought you were finished. 24 A. "Even if one has inherited a</p>	<p style="text-align: right;">Page 88</p> <p>1 from either Dr. Levy's report or from 2 somewhere -- some other source? 3 A. The thoughts are the same. 4 The words seem to be identical. And 5 again, if you interpret that one way and 6 I interpret it another, I certainly do 7 not interpret it as plagiarism. 8 Q. Let me show you another 9 example. 10 (Document marked for 11 identification as Exhibit 12 Zelikoff-14.) 13 BY MR. HEGARTY: 14 Q. I'm going to mark as 15 Exhibit 14, again a portion of your 16 report Page 12 and a portion of a report 17 by Rebecca Smith-Bindman. Do you know 18 who that is? 19 A. Not at all. 20 Q. Did you see her report in 21 this case before preparing your report? 22 A. I never looked at her 23 report. 24 Q. If you would look at the two</p>
<p style="text-align: right;">Page 87</p> <p>1 genetic mutation that predisposes one's 2 chances, doesn't mean he or she has to 3 get cancer." Again, common knowledge 4 from everyone. 5 Q. Well, Dr. Zelikoff, my 6 question is different than that. 7 My question is, can you 8 explain to us here today, given that you 9 did not see Dr. Levy's report until after 10 you completed your report, how you have 11 several identical sentences between your 12 report and Dr. Levy's report? 13 MS. O'DELL: Object to the 14 form. 15 BY MR. HEGARTY: 16 Q. Dr. Levy's report. 17 A. I cannot -- I -- I don't 18 know. The only -- what I can say is that 19 there was likely a publication. But that 20 is speculation, because I have not looked 21 that over. 22 Q. But is it your testimony 23 here today that the words in your report 24 were solely your own words and not taken</p>	<p style="text-align: right;">Page 89</p> <p>1 reports side by side under the 2 definition -- under the heading 3 Fragrances -- 4 A. I'm sorry, I don't have her 5 report. 6 Q. You have one page of her 7 report in that exhibit. You have the -- 8 the front page and the one page of her 9 report, and you have Page 12 of your 10 report, correct? 11 A. I see. Correct. 12 Q. Do you see that the section 13 under the heading Fragrances is identical 14 between the two reports? 15 A. Yes. They are identical 16 wording. 17 Q. And none of those sentences 18 are common knowledge, correct? 19 MS. O'DELL: Object to the 20 form. 21 THE WITNESS: It's a 22 statement. 23 BY MR. HEGARTY: 24 Q. But it's not common</p>

<p style="text-align: right;">Page 90</p> <p>1 knowledge, correct, Doctor?</p> <p>2 A. But it's a -- it is -- there</p> <p>3 are more than 150 different chemicals</p> <p>4 added to Johnson's Baby Powder and Shower</p> <p>5 to Shower products. I reviewed the</p> <p>6 expert report from Dr. Crowley that</p> <p>7 concludes that some of these chemicals</p> <p>8 may contribute to the inflammatory</p> <p>9 response, toxicity, and potential</p> <p>10 carcinogenicity. I concur with his</p> <p>11 opinion.</p> <p>12 I say the same thing as</p> <p>13 Dr. Smith-Bindman.</p> <p>14 Q. Is it your testimony that</p> <p>15 you and Dr. Smith-Bindman came to the</p> <p>16 exact same words just by coincidence?</p> <p>17 MS. O'DELL: Object to the</p> <p>18 form.</p> <p>19 THE WITNESS: We came to the</p> <p>20 same conclusions.</p> <p>21 BY MR. HEGARTY:</p> <p>22 Q. That's not my question. My</p> <p>23 question is, is it your testimony here</p> <p>24 today that you and Dr. Smith-Bindman came</p>	<p style="text-align: right;">Page 92</p> <p>1 Q. Sure. Is it your testimony</p> <p>2 that the words in your report under</p> <p>3 section -- under the section Fragrances</p> <p>4 are your words and your words alone from</p> <p>5 no other source?</p> <p>6 MS. O'DELL: Object to the</p> <p>7 form.</p> <p>8 THE WITNESS: I don't quite</p> <p>9 understand what you mean by no</p> <p>10 other source.</p> <p>11 These are my words. They</p> <p>12 confer my opinion.</p> <p>13 BY MR. HEGARTY:</p> <p>14 Q. Well, did you copy those</p> <p>15 words from some source besides</p> <p>16 Smith-Bindman's report?</p> <p>17 A. I did not copy words. I --</p> <p>18 I don't know how this happened.</p> <p>19 If I was in error, I own</p> <p>20 that responsibility.</p> <p>21 (Document marked for</p> <p>22 identification as Exhibit</p> <p>23 Zelikoff-15.)</p> <p>24 BY MR. HEGARTY:</p>
<p style="text-align: right;">Page 91</p> <p>1 to the exact -- to say the exact same</p> <p>2 thing under the section Fragrance simply</p> <p>3 by coincidence?</p> <p>4 MS. O'DELL: Objection to</p> <p>5 form.</p> <p>6 THE WITNESS: I don't do</p> <p>7 anything usually by coincidence.</p> <p>8 BY MR. HEGARTY:</p> <p>9 Q. Okay. Is it your testimony</p> <p>10 that the words that you wrote under the</p> <p>11 section Fragrances on Page 12 are your</p> <p>12 words and came from nowhere else?</p> <p>13 A. I don't quite understand</p> <p>14 where they could have come from because I</p> <p>15 did not review her report.</p> <p>16 Q. Is it your testimony that</p> <p>17 the words in your report under the</p> <p>18 section Fragrances are your words and</p> <p>19 your words alone from no other source?</p> <p>20 MS. O'DELL: Object to the</p> <p>21 form.</p> <p>22 THE WITNESS: Could you</p> <p>23 please repeat the question?</p> <p>24 BY MR. HEGARTY:</p>	<p style="text-align: right;">Page 93</p> <p>1 Q. I'm going to show you what</p> <p>2 I'm next marking as Exhibit 15.</p> <p>3 MS. O'DELL: Is this one</p> <p>4 exhibit?</p> <p>5 MR. HEGARTY: That's one</p> <p>6 exhibit.</p> <p>7 BY MR. HEGARTY:</p> <p>8 Q. Doctor, Exhibit Number 15 is</p> <p>9 again a portion of your report, and also</p> <p>10 attached to it is a reference from</p> <p>11 Genetics Home Reference dated June 27,</p> <p>12 2017. Do you see both documents?</p> <p>13 A. I do see both documents.</p> <p>14 Q. We have highlighted and</p> <p>15 numbered in Exhibit 15 the portions from</p> <p>16 your report which are taken word for word</p> <p>17 from Genetics Home Reference without a</p> <p>18 single reference to that authority</p> <p>19 anywhere in your report, including in the</p> <p>20 materials considered or reviewed.</p> <p>21 MS. O'DELL: Objection.</p> <p>22 BY MR. HEGARTY:</p> <p>23 Q. Do you see that?</p> <p>24 MS. O'DELL: Objection to</p>

<p style="text-align: right;">Page 94</p> <p>1 form.</p> <p>2 And -- and, Doctor, take a</p> <p>3 moment to review both, because the</p> <p>4 way this is put together is a</p> <p>5 little confusing.</p> <p>6 THE WITNESS: I see what</p> <p>7 you're referring to.</p> <p>8 BY MR. HEGARTY:</p> <p>9 Q. And did you copy, for</p> <p>10 purposes of your report, without citation</p> <p>11 to this authority, the words that we've</p> <p>12 identified from this reference to Genetic</p> <p>13 Home Reference?</p> <p>14 MS. O'DELL: Objection to</p> <p>15 the form.</p> <p>16 THE WITNESS: So when you</p> <p>17 have things like, "Inherited</p> <p>18 mutations are passed down from</p> <p>19 parent to child and are present</p> <p>20 throughout a person's life in</p> <p>21 virtually in every cell of the</p> <p>22 body." Biology 101, basically,</p> <p>23 where that came from.</p> <p>24 "These mutations are called</p>	<p style="text-align: right;">Page 96</p> <p>1 your report in this case?</p> <p>2 A. I may have used -- it</p> <p>3 appears that I have used the same words.</p> <p>4 And if I did that, which it</p> <p>5 appears that I have, then I've done it</p> <p>6 with the intent to get those same points</p> <p>7 across.</p> <p>8 Q. But you do agree that you</p> <p>9 have included in your report a sequence</p> <p>10 of words incorporated from another source</p> <p>11 without quotation marks, correct?</p> <p>12 MS. O'DELL: Objection to</p> <p>13 form.</p> <p>14 THE WITNESS: I don't use --</p> <p>15 I don't usually use quotation</p> <p>16 marks.</p> <p>17 BY MR. HEGARTY:</p> <p>18 Q. Well, you have used other</p> <p>19 people's words without acknowledging</p> <p>20 where they came from, correct?</p> <p>21 MS. O'DELL: Object to the</p> <p>22 form.</p> <p>23 THE WITNESS: I could have</p> <p>24 used quotation marks. And if I</p>
<p style="text-align: right;">Page 95</p> <p>1 germ line mutations because</p> <p>2 they're present in the parents'</p> <p>3 egg or sperm, a germ cell."</p> <p>4 Yes, some of these sentences</p> <p>5 appear to be the same as what is</p> <p>6 in here.</p> <p>7 However, again, I stand on</p> <p>8 the fact that all of these -- all</p> <p>9 of my statements are common</p> <p>10 knowledge that have come from</p> <p>11 numerous references. Although the</p> <p>12 words may be the same, the</p> <p>13 thoughts are -- are said as well</p> <p>14 as they can be said.</p> <p>15 BY MR. HEGARTY:</p> <p>16 Q. Dr. Zelikoff, have you ever</p> <p>17 seen this reference to Genetic Home</p> <p>18 Reference before right now?</p> <p>19 A. Not to my knowledge.</p> <p>20 Q. So is it your testimony that</p> <p>21 you did not copy the words from Genetic</p> <p>22 Home Reference that we have highlighted</p> <p>23 that correspond by number to the portions</p> <p>24 in your report for purposes of preparing</p>	<p style="text-align: right;">Page 97</p> <p>1 were to do this over, I would use</p> <p>2 quotation marks.</p> <p>3 BY MR. HEGARTY:</p> <p>4 Q. You're not telling us,</p> <p>5 Doctor, that if you prepared an article</p> <p>6 for publication in a journal, that you</p> <p>7 would take references from another source</p> <p>8 like Genetic Home Reference, include them</p> <p>9 in the article, verbatim, not use</p> <p>10 quotation marks and not reference that</p> <p>11 cite. Is that what you're saying?</p> <p>12 MS. O'DELL: Objection to</p> <p>13 form.</p> <p>14 THE WITNESS: I'm standing</p> <p>15 on my interpretation, and that is</p> <p>16 that in a reference that I would</p> <p>17 prepare in a publication, it would</p> <p>18 be accepted for peer review if</p> <p>19 there was something that I felt</p> <p>20 was common knowledge, that I would</p> <p>21 not reference it.</p> <p>22 To your point, if I had to</p> <p>23 do this over, I would have put</p> <p>24 quotation marks around this.</p>

<p style="text-align: right;">Page 98</p> <p>1 BY MR. HEGARTY:</p> <p>2 Q. You would have cited to the</p> <p>3 authority, as well, from which that --</p> <p>4 those passages were lifted, correct?</p> <p>5 MS. O'DELL: Objection to</p> <p>6 form.</p> <p>7 THE WITNESS: I certainly</p> <p>8 could if that was a concern from</p> <p>9 the journal or from the reviewer,</p> <p>10 then I would definitely put in the</p> <p>11 reference.</p> <p>12 BY MR. HEGARTY:</p> <p>13 Q. If a student had prepared</p> <p>14 this, and you became aware that the</p> <p>15 student had lifted portions from Genetic</p> <p>16 Home Reference without any citation,</p> <p>17 without acknowledging where it came from,</p> <p>18 would that be okay with you?</p> <p>19 MS. O'DELL: Objection to</p> <p>20 form.</p> <p>21 THE WITNESS: There are --</p> <p>22 this is a large document. And in</p> <p>23 order for something to be copied</p> <p>24 or, as you put it, plagiarized,</p>	<p style="text-align: right;">Page 100</p> <p>1 will not -- this is the -- what</p> <p>2 you gave me was an interpretation,</p> <p>3 was NYU policy, an interpretation</p> <p>4 of that, which is not the same as</p> <p>5 mine.</p> <p>6 BY MR. HEGARTY:</p> <p>7 Q. Well, you do agree, though,</p> <p>8 that between the -- your report, the</p> <p>9 portions taken from your report and the</p> <p>10 Genetic Home Reference reference are</p> <p>11 identical?</p> <p>12 MS. O'DELL: Object to the</p> <p>13 form.</p> <p>14 THE WITNESS: I agree that</p> <p>15 there are sentences that are</p> <p>16 identical. Yes.</p> <p>17 BY MR. HEGARTY:</p> <p>18 Q. You did not acknowledge that</p> <p>19 source anywhere in your report, correct?</p> <p>20 A. If you say so.</p> <p>21 Q. Do you think that's okay to</p> <p>22 do that?</p> <p>23 MS. O'DELL: Objection to</p> <p>24 form.</p>
<p style="text-align: right;">Page 99</p> <p>1 there has to be a certain amount</p> <p>2 or percentage of the document that</p> <p>3 has to be the same.</p> <p>4 And this document, my</p> <p>5 report, is quite large. So if a</p> <p>6 student prepared this, and their</p> <p>7 term paper, for example, was 50</p> <p>8 pages, I would let them know that</p> <p>9 if prepared the next time they</p> <p>10 might want to put in a reference.</p> <p>11 But I would have to look at</p> <p>12 the entire size of the document</p> <p>13 and the percentage of it which had</p> <p>14 similar -- similar statements and</p> <p>15 sentences.</p> <p>16 BY MR. HEGARTY:</p> <p>17 Q. You do agree that under the</p> <p>18 policy we marked, we're talking about</p> <p>19 what you did with regard to this Genetics</p> <p>20 Home Reference cite, meets the definition</p> <p>21 of plagiarism?</p> <p>22 MS. O'DELL: Objection to</p> <p>23 form.</p> <p>24 THE WITNESS: I certainly</p>	<p style="text-align: right;">Page 101</p> <p>1 THE WITNESS: If I had not</p> <p>2 thought it was okay, I would not</p> <p>3 have done it.</p> <p>4 BY MR. HEGARTY:</p> <p>5 Q. Would that -- would that be</p> <p>6 acceptable for purposes of publishing</p> <p>7 your report?</p> <p>8 MS. O'DELL: Objection to</p> <p>9 the form.</p> <p>10 THE WITNESS: My opinion</p> <p>11 stands. And that is my</p> <p>12 interpretation of what is okay to</p> <p>13 do based on common knowledge and</p> <p>14 multiple sources, stands the same.</p> <p>15 BY MR. HEGARTY:</p> <p>16 Q. If you were to publish your</p> <p>17 report, as it is, would you go back and</p> <p>18 use quotation marks and cite the</p> <p>19 reference that we just looked at --</p> <p>20 A. If I had --</p> <p>21 Q. -- Exhibit Number 16?</p> <p>22 MS. O'DELL: Excuse me,</p> <p>23 Doctor. Just let him finish.</p> <p>24 THE WITNESS: Of course.</p>

<p style="text-align: right;">Page 102</p> <p>1 I'm sorry.</p> <p>2 MS. O'DELL: Thank you. And</p> <p>3 just give me a moment to object.</p> <p>4 Thank you.</p> <p>5 BY MR. HEGARTY:</p> <p>6 Q. Did you hear my question?</p> <p>7 A. Could you repeat your</p> <p>8 question, please?</p> <p>9 Q. Sure. If you were to</p> <p>10 publish a report as it is, would you go</p> <p>11 back and use quotation marks and cite the</p> <p>12 reference that we just looked at in</p> <p>13 Exhibit Number 16?</p> <p>14 A. Now that you've pointed out</p> <p>15 your interpretation of it, I would</p> <p>16 certainly consider that.</p> <p>17 (Document marked for</p> <p>18 identification as Exhibit</p> <p>19 Zelikoff-16.)</p> <p>20 BY MR. HEGARTY:</p> <p>21 Q. Let me show you what I'm</p> <p>22 next marking as Exhibit Number 16.</p> <p>23 MS. O'DELL: I'll reach</p> <p>24 over, instead of you throwing it.</p>	<p style="text-align: right;">Page 104</p> <p>1 increased release of ROS."</p> <p>2 That is a very common --</p> <p>3 commonly known point.</p> <p>4 BY MR. HEGARTY:</p> <p>5 Q. How about Point Number 4 in</p> <p>6 the abstract?</p> <p>7 A. As --</p> <p>8 Q. That's -- is it your</p> <p>9 testimony that Point Number 4 in the</p> <p>10 abstract is what you consider common</p> <p>11 knowledge?</p> <p>12 A. "Activation of the</p> <p>13 transcription factors can lead to the</p> <p>14 expression of over 500 genes, including</p> <p>15 more for growth factors." And I'm going</p> <p>16 to read the entire abstract.</p> <p>17 Actually this is a review</p> <p>18 paper. And this is not a unique finding</p> <p>19 to this particular author.</p> <p>20 And thus "Activation of</p> <p>21 transcription factors," again as I read,</p> <p>22 is an outcome of many, many authors. And</p> <p>23 as I said, is a review paper, not a</p> <p>24 unique investigator-initiated outcome.</p>
<p style="text-align: right;">Page 103</p> <p>1 BY MR. HEGARTY:</p> <p>2 Q. This is another portion of</p> <p>3 your report which we've correspondingly</p> <p>4 referenced to an article by Simone</p> <p>5 Reuter. And you can see where we've</p> <p>6 identified six different times where</p> <p>7 sentences have been copied verbatim from</p> <p>8 this article without any quotation or any</p> <p>9 acknowledgment of its -- of the source.</p> <p>10 Do you see that?</p> <p>11 MS. O'DELL: Object --</p> <p>12 excuse me. Object to the form.</p> <p>13 Feel free to review it, the</p> <p>14 reference or the exhibit. There</p> <p>15 are two things paper clipped</p> <p>16 together, if you need to look at</p> <p>17 it in more detail.</p> <p>18 THE WITNESS: Again, there</p> <p>19 are sentences such as, "During</p> <p>20 inflammation macrophages, mast</p> <p>21 cells, and neutrophils were</p> <p>22 recruited at the site of damage,</p> <p>23 leads to a respiratory burst and</p> <p>24 increased uptake of oxygen, and an</p>	<p style="text-align: right;">Page 105</p> <p>1 Q. You keep referring to common</p> <p>2 knowledge. Who is -- who has this common</p> <p>3 knowledge?</p> <p>4 A. People who read scientific</p> <p>5 journals.</p> <p>6 Q. So is it your testimony that</p> <p>7 someone who would read your report would</p> <p>8 understand that that is not -- those are</p> <p>9 not your words but taken from</p> <p>10 somewhere -- somewhere else?</p> <p>11 MS. O'DELL: Object to the</p> <p>12 form.</p> <p>13 THE WITNESS: It would</p> <p>14 depend upon who is reading it.</p> <p>15 BY MR. HEGARTY:</p> <p>16 Q. Can you cite for me any</p> <p>17 publication that you have ever written</p> <p>18 where you have cited another authority</p> <p>19 word for word and did not use quotation</p> <p>20 marks and did not reference that</p> <p>21 authority?</p> <p>22 A. Not off the top of my head.</p> <p>23 Q. But you did do that in your</p> <p>24 expert report in this case, correct?</p>

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1 MS. O'DELL: Object to the
2 form.
3 THE WITNESS: It appears
4 from what you're showing me, that
5 in my interpretation of common
6 knowledge and multiple -- multiple
7 investigators, I have done that,
8 yes.
9 (Document marked for
10 identification as Exhibit
11 Zelikoff-17.)
12 BY MR. HEGARTY:
13 Q. I'm going to mark next
14 Exhibit Number 17, another portion of
15 your report where you, again, take
16 sentences from a publication called
17 EnvironmentalChemistry.com.
18 You cite them word for word
19 in your report and you make no reference
20 anywhere in your report to this
21 authority.
22 A. I said --
23 MS. O'DELL: Excuse me.
24 Excuse Me, Doctor. Excuse me.

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1 MR. HEGARTY: I'm not
2 finished with my question.
3 MS. O'DELL: I thought you
4 were finished with your question.
5 MR. HEGARTY: Because I just
6 made a statement.
7 MS. O'DELL: Well, I object
8 to the statement. You ask your
9 question, and I'll probably object
10 to that.
11 But give me a chance, the
12 two of you, please.
13 BY MR. HEGARTY:
14 Q. Let me -- Doctor, this --
15 the reference that we have here in the
16 Exhibit Number 17 is to a website called
17 EnvironmentalChemistry.com. Did you
18 review this website in preparing your
19 report?
20 A. I don't recall.
21 Q. Do you see where we make
22 reference to five different places where
23 you copied word for word from
24 EnvironmentalChemistry.com?

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1 MS. O'DELL: Object to the
2 form.
3 THE WITNESS: Yes, I see
4 what you're saying.
5 BY MR. HEGARTY:
6 Q. And nowhere in your report
7 do you give acknowledgment to
8 EnvironmentalChemistry.com as a source of
9 the information that you copied, correct?
10 MS. O'DELL: Object to the
11 form.
12 THE WITNESS: I do say the
13 U.S. EPA defines asbestos by
14 limiting the term to six specific
15 fibrous minerals from two distinct
16 groups. And I go on from there.
17 That is a referral to the U.S.
18 EPA.
19 BY MR. HEGARTY:
20 Q. Doctor, nowhere in your
21 report, in those notebooks or anywhere do
22 you cite to EnvironmentalChemistry.com,
23 do you?
24 MS. O'DELL: Object. Object

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1 to the form.
2 THE WITNESS: Not to my
3 knowledge.
4 EnvironmentalChemistry.com, I
5 don't even recall reviewing it.
6 BY MR. HEGARTY:
7 Q. But don't you agree that you
8 would have had to review it based on the
9 fact that there are identical sentences
10 taken from -- that are identical
11 sentences, in Environmental Chemistry and
12 in your report?
13 MS. O'DELL: Object to the
14 form.
15 THE WITNESS: This -- again,
16 this information is common
17 knowledge. This is not a creation
18 of EnvironmentalChemistry.com.
19 They are not an individual
20 investigator finding this data.
21 They are reporting this data on
22 the internet for people's review.
23 BY MR. HEGARTY:
24 Q. Is

<p style="text-align: right;">Page 110</p> <p>1 EnvironmentalChemistry.com a reliable 2 authority? 3 MS. O'DELL: Object to the 4 form. 5 THE WITNESS: I have no 6 idea -- sorry. 7 MS. O'DELL: Go ahead. 8 THE WITNESS: I have no idea 9 of the impact factor or the 10 reliability of this. However, in 11 talking about this, and saying the 12 things that I -- that you have 13 said I have used identically, 14 which appear to be the case -- 15 "while amphibole and serpentine 16 asbestos may have fibrous habits, 17 they have very different forms. 18 Amphibole are double-chain 19 silicates." 20 This is known in the 21 asbestos -- in the asbestos 22 literature. And the basic 23 structural unit is silicone oxide. 24 This is not Environmental</p>	<p style="text-align: right;">Page 112</p> <p>1 published methodology which says that 2 your interpretation of what you are to 3 quote and what you are to cite in an 4 article is an accepted methodology in 5 publishing scientific literature? 6 A. It's my professional opinion 7 after 30 years of work. 8 Q. Well, can you cite for me 9 any published authority that says your 10 definition of what you are to cite and 11 what you are to reference is the 12 definition that's applicable to medical 13 literature? 14 MS. O'DELL: Objection to 15 form. 16 THE WITNESS: I have never 17 been accused or cited by any 18 publication in any of my 135 19 papers or my over 30 book chapters 20 of having anything that was of a 21 dubious nature, ever. 22 BY MR. HEGARTY: 23 Q. That's not my question. My 24 question was can you cite for me any</p>
<p style="text-align: right;">Page 111</p> <p>1 Chemistry's individual 2 investigator initiated. 3 I think you may be confusing 4 an individual paper where an 5 investigator sits down in the 6 laboratory and works out or comes 7 up with a fact and that it's his. 8 As opposed to data that's just out 9 there in the internet, out there 10 in the world, out there in book 11 chapters, out there everywhere, 12 that people know. 13 This is not an investigator 14 initiated, whether it's 15 EnvironmentalChemistry.com. 16 So I will -- I will say to 17 you that in many cases, I did use 18 the same sentence. Certainly 19 EnvironmentalChemistry.com is not 20 an investigator-initiated point of 21 reference. It's just facts that 22 are supported by other experts. 23 BY MR. HEGARTY: 24 Q. Can you cite for me any</p>	<p style="text-align: right;">Page 113</p> <p>1 written authority that says that in 2 publishing medical literature, if you're 3 citing what you call general knowledge 4 word for word from another source, you 5 don't have to quote it and you do not 6 have to give it any reference. 7 A. Just my professional opinion 8 of 30 years of work. 9 Q. Okay. And in a -- and 10 you've never done that in any medical 11 article you -- any article you have 12 published, correct? 13 A. I cannot -- I cannot speak 14 to all. 15 Q. Well, if you were to write a 16 medical article -- a scientific article 17 today, and you were to quote something 18 from -- take something word for word from 19 EnvironmentalChemistry.com, is it your 20 testimony you wouldn't give any reference 21 to it or wouldn't use quotation marks? 22 MS. O'DELL: Object to the 23 form. 24 THE WITNESS: I -- I stand</p>

<p style="text-align: right;">Page 114</p> <p>1 on the opinion that I have, that</p> <p>2 it would be common knowledge.</p> <p>3 BY MR. HEGARTY:</p> <p>4 Q. That's not my question. My</p> <p>5 question is if you were to write an</p> <p>6 article today and you were to cite</p> <p>7 Environmental.com word for word, is it</p> <p>8 your testimony you would not quote</p> <p>9 that -- those words or give any reference</p> <p>10 or acknowledgment to environmental --</p> <p>11 to --</p> <p>12 A. EnvironmentalChemistry.com.</p> <p>13 Q. EnvironmentalChemistry.com?</p> <p>14 MS. O'DELL: Object to the</p> <p>15 form.</p> <p>16 THE WITNESS: I would do the</p> <p>17 same thing I've done for this</p> <p>18 report.</p> <p>19 BY MR. HEGARTY:</p> <p>20 Q. Okay. And is that true for</p> <p>21 every resource that we've looked at so</p> <p>22 far? You would -- if you were to write a</p> <p>23 scientific journal today, you would --</p> <p>24 and quoted from all those resources, you</p>	<p style="text-align: right;">Page 116</p> <p>1 that you have copied verbatim from that</p> <p>2 publication without giving any</p> <p>3 acknowledgment to Dr. Rakoff-Nahoum or</p> <p>4 use any quotation marks. Do you see</p> <p>5 that?</p> <p>6 MS. O'DELL: Object to the</p> <p>7 form.</p> <p>8 THE WITNESS: So on Page 124</p> <p>9 of the review by Seth</p> <p>10 Rakoff-Nahoum -- Nahoum, if you</p> <p>11 look on -- under cancer and</p> <p>12 inflammation, and one of the</p> <p>13 points that you make here -- and</p> <p>14 by the way, this is a review</p> <p>15 paper, again not an independent</p> <p>16 investigator-initiated data from</p> <p>17 the laboratory -- "Epidemiological</p> <p>18 evidence points to a connection</p> <p>19 between inflammation and" -- "and</p> <p>20 predisposition for the development</p> <p>21 of cancer, i.e., long-term</p> <p>22 inflammation leads to the</p> <p>23 development of dysplasia," there's</p> <p>24 no reference there.</p>
<p style="text-align: right;">Page 115</p> <p>1 would not use quotation marks and you</p> <p>2 would not give any acknowledgment in</p> <p>3 any -- if you were to write a scientific</p> <p>4 article today?</p> <p>5 MS. O'DELL: Object to form.</p> <p>6 Misstates her testimony.</p> <p>7 THE WITNESS: I -- I did say</p> <p>8 that there are certain cases that</p> <p>9 if I had to do it over and based</p> <p>10 upon your rigorous opinion of</p> <p>11 this, that I would place quotation</p> <p>12 marks or add a reference, yes.</p> <p>13 (Document marked for</p> <p>14 identification as Exhibit</p> <p>15 Zelikoff-18.)</p> <p>16 BY MR. HEGARTY:</p> <p>17 Q. I'm going to show you what</p> <p>18 I'm next marking as Exhibit 18.</p> <p>19 This is another portion of</p> <p>20 your report. In addition to that</p> <p>21 exhibit -- or with that exhibit is a</p> <p>22 reference to a publication by</p> <p>23 Rakoff-Nahoum, where you again made</p> <p>24 references to four different sentences</p>	<p style="text-align: right;">Page 117</p> <p>1 So this author also,</p> <p>2 Dr. Rakoff-Nahoum -- sorry, I'm</p> <p>3 murdering his name -- also gives</p> <p>4 no reference to that.</p> <p>5 Again, in this case, using</p> <p>6 my analogy of something that has</p> <p>7 been gathered by numerous other</p> <p>8 investigators and is common</p> <p>9 knowledge to the -- to the</p> <p>10 scientific population, he did also</p> <p>11 not use a reference. And I did</p> <p>12 not use a reference.</p> <p>13 BY MR. HEGARTY:</p> <p>14 Q. But if -- but if you look at</p> <p>15 his -- the last reference, Number 4, he</p> <p>16 does acknowledge a resource for all of</p> <p>17 those statements, Resource 20 in the</p> <p>18 publication, correct?</p> <p>19 MS. O'DELL: Objection.</p> <p>20 Could you provide, if you're</p> <p>21 going to use this exhibit, provide</p> <p>22 the full manuscript that</p> <p>23 identifies Resource 20.</p> <p>24 (Document marked for</p>

<p style="text-align: right;">Page 118</p> <p>1 identification as Exhibit 2 Zelickoff-20.) 3 BY MR. HEGARTY: 4 Q. I'll mark as 20, the 5 entirety of the Rakoff-Nahoum article, 6 which does include 20, which is a 7 reference to Hussain, "Radical Causes of 8 Cancer." 9 A. Citation 20 in Exhibit 20 is 10 also a review paper, and none of these 11 references are going back to the 12 independent investigator who actually 13 said this. 14 So these are reviewed in. 15 Again, standing by my opinion that 16 oftentimes in review articles which -- 17 in -- in review articles, they often take 18 the liberty, as seen in your first point, 19 that you do not use a reference. 20 Now, I would have to read 21 Reference 20 in order to see whether 22 that, in fact, reviews Points 2, 3 and 4 23 in your "Why Cancer and Inflammation" 24 paper.</p>	<p style="text-align: right;">Page 120</p> <p>1 publication by OSHA for purposes of your 2 report. Do you see that? 3 MS. O'DELL: Objection to 4 form. 5 THE WITNESS: I do see what 6 you're pointing to. I also will 7 tell you that Point 1 that you 8 point out in the OSHA United 9 States Department of Labor, on 10 hexavalent chromium, which is off 11 the internet, adverse health 12 effects associated, yes, I used 13 adverse health -- health effects 14 other than cancer, and then I had 15 these different words. 16 I'm just explaining what I 17 see. 18 With chromium-6, hexavalent 19 chromium exposure include 20 occupational asthma, eye 21 irritation and damage, perforated 22 ear drums, et cetera, et cetera. 23 This can be found in numerous, 24 numerous references. This again</p>
<p style="text-align: right;">Page 119</p> <p>1 I do not know that 2 Reference 20 actually reviews all of 3 these points and are the reference. 4 Also, many of these 5 points -- and again, another review 6 paper. 7 Many of these points, the 8 chronic inflammatory states associated 9 with infection, irritation, may lead to 10 environments that foster genomic lesions 11 in tumor initiation, no reference there. 12 One effect and mechanism, et 13 cetera, et cetera. Hydroxyl radicals, 14 reactive oxygen species, no reference 15 there. No quotation marks. 16 So I don't know whether he, 17 in fact, uses the same logic that I did. 18 (Document marked for 19 identification as Exhibit 20 Zelickoff-19.) 21 BY MR. HEGARTY: 22 Q. I'm going to show you 23 Exhibit 19. This is another reference 24 where you copied portions of a</p>	<p style="text-align: right;">Page 121</p> <p>1 is common knowledge for anyone 2 doing chromium -- chromium 3 studies. 4 Again, did I use the same 5 words? In many cases, I did here. 6 "Can also develop an 7 allergic skin reaction called 8 allergic contact dermatitis." I'm 9 not quite sure how else you can 10 say that, that phrase. 11 So I still feel confident in 12 what I did was based upon my 13 professional judgment. 14 (Document marked for 15 identification as Exhibit 16 Zelickoff-21.) 17 BY MR. HEGARTY: 18 Q. Okay. I'll show you what I 19 next marked as Exhibit 21. Exhibit 21 is 20 again a portion of your report where we 21 have identified statements that are taken 22 verbatim without acknowledgment from the 23 publication attached thereto by Kasprzak. 24 A. Kasprzak. I'm sorry, sir.</p>

<p style="text-align: right;">Page 122</p> <p>1 MS. O'DELL: Did you finish 2 your question? 3 BY MR. HEGARTY: 4 Q. No. Do you see where I'm 5 talk -- do you see where I'm referencing? 6 MS. O'DELL: Object to form. 7 THE WITNESS: I -- 8 MS. O'DELL: Take a moment 9 if you need to, Doctor. 10 THE WITNESS: So what I see 11 in the abstract of a paper, a 12 review paper called Nickel 13 Carcinogenesis by Kasprzak and 14 Sunderman and Konstantine 15 Salnikow, you say -- you're 16 pointing to, "The exact mechanisms 17 of nickel-induced carcinogenesis 18 are not known and have been 19 subject of numerous 20 epidemiological and experimental 21 investigations." 22 That is not -- that -- okay. 23 And what's in my paper is, "The 24 exact mechanisms of nickel-induced</p>	<p style="text-align: right;">Page 124</p> <p>1 risks are primarily related to 2 exposure to soluble nickel 3 concentrations," et cetera, et 4 cetera. 5 But in many cases throughout 6 this reference, I can also -- it 7 being a review paper, I can also 8 tell you there's epidemiological 9 evidence on possible cancer risk 10 from general environment and 11 dietary nickel exposures not cited 12 as a reference, not quoted. 13 BY MR. HEGARTY: 14 Q. Are you finished? 15 A. I am, thank you. 16 THE WITNESS: Excuse me. 17 May I just point out that it's 18 getting even colder in here and 19 I'm a bit uncomfortable. 20 (Whereupon, a discussion was 21 held off the record.) 22 THE WITNESS: May I go get 23 my scarf? 24 MR. HEGARTY: Off the</p>
<p style="text-align: right;">Page 123</p> <p>1 cainogenesis are not known but 2 likely involve genetic and 3 epigenetic routes." 4 That's not the same as this 5 sentence. It has portions of the 6 same, but not the entire sentence 7 is the same. 8 "Are likely to evolve 9 genetic and epigenetic routes." 10 Not quite sure how else you would 11 say this. 12 And this again is a review 13 paper. And going through it, here 14 I can cite a sentence. 15 "Occupational exposure to nickel 16 occurs predominately in mining, 17 refining, alloy production, 18 electroplating, and welding." 19 This is in the review by Kasprzak. 20 There's no reference there either. 21 In this sentence, "In 1990 22 the International Committee on 23 Nickel Carcinogenesis in Man 24 suggested that respiratory cancer</p>	<p style="text-align: right;">Page 125</p> <p>1 record. 2 THE VIDEOGRAPHER: The time 3 is 11:11 a.m. Off the record. 4 (Short break.) 5 THE VIDEOGRAPHER: The time 6 is 11:23 a.m. Back on record. 7 (Documents marked for 8 identification as Exhibits 9 Zelickoff-25 through 32.) 10 MR. HEGARTY: We're back on 11 the record. I'm going to mark -- 12 I've marked as Exhibits 25 through 13 32, other examples taken from 14 Dr. Zelickoff's report where -- 15 along with the references to which 16 they were taken. And I'm just 17 going to mark those for purposes 18 of the deposition as those 19 exhibits. 20 MS. O'DELL: What's the 21 exhibit number? 22 MR. HEGARTY: Exhibits 25 23 through 32, and I did skip over 24 through 22 through 24, but I'll</p>

<p style="text-align: right;">Page 126</p> <p>1 come back to it. So we did get 2 kind of out of order in the way I 3 marked those. 4 MS. O'DELL: So plaintiff 5 objects to the Exhibit 25 through 6 32 being added to the record. 7 There's no testimony from 8 Dr. Zelikoff. So any assertion 9 that counsel has made that those 10 are relevant, we would object 11 and -- and oppose their being 12 included. 13 BY MR. HEGARTY: 14 Q. Doctor, if you would look at 15 your report which is Exhibit Number 2. 16 A. Yes, sir. 17 Q. On Page 2 of your report, 18 under the section Mandate and 19 Methodology? 20 A. Yes, sir, I see it. 21 Q. You say your mandate was to 22 look at the scientific literature and 23 assess whether there is biologic 24 plausibility for talc to cause ovarian</p>	<p style="text-align: right;">Page 128</p> <p>1 A. That was my -- that was -- 2 the request was to assess biological 3 plausibility. 4 Q. You say in that portion that 5 we just reviewed that -- you say for the 6 increased risk of ovarian cancer with 7 talc use. Did you assume for purposes of 8 your report that there is, in fact, an 9 increased risk of ovarian cancer with 10 talc use? 11 A. I'm sorry, sir, can you tell 12 me exactly which paragraph? 13 Q. In the first paragraph under 14 the section Mandate and Methodology, you 15 say "assess whether there is biologic 16 plausibility" -- "biologically plausible 17 explanation for the increased risk of 18 ovarian cancer with the perineal use of 19 talcum powder products." 20 Do you see that? See where 21 I'm reading? 22 A. I am sorry, sir, I do not. 23 Q. First paragraph under 24 page -- on Page 2 under mandate and</p>
<p style="text-align: right;">Page 127</p> <p>1 cancer from perineal use; is that 2 correct? 3 MR. GOLOMB: I'm sorry. 4 What page are you on? 5 MR. HEGARTY: Page 2. 6 THE WITNESS: Are you done? 7 BY MR. HEGARTY: 8 Q. Yes. 9 A. My mandate was to review the 10 scientific literature and assess whether 11 there was biological plausible 12 explanation for the increased risk of 13 ovarian cancer with perineal use of 14 talcum powder products, yes, that is 15 correct. 16 Q. Who gave you that mandate? 17 A. That was the plaintiff 18 attorney, Ms. Emory [sic] and Ms. O'Dell. 19 Q. You say -- 20 A. They -- I -- but let me add 21 they -- when you say gave me that 22 mandate, can you explain what you mean by 23 gave me that mandate? 24 Q. Well, from --</p>	<p style="text-align: right;">Page 129</p> <p>1 methodology. 2 A. Is that the notion of 3 biological plausibility paragraph, or are 4 you -- 5 Q. It's the first paragraph 6 under the section Mandate and 7 Methodology. 8 A. Well, sir, there are two, 9 two paragraphs. One says mandate. I was 10 asked to review the scientific 11 literature. Then there is another 12 paragraph that says the notion of 13 biological plausibility is 14 multifactorial. 15 Q. Doctor, if you'd listen to 16 my question. I said the first paragraph 17 under mandate and methodology. Do you 18 understand that? 19 A. I do not -- I do not see it 20 and you can -- 21 Q. You don't see the first 22 paragraph that begins mandate? 23 A. I just read that to you, 24 sir.</p>

<p style="text-align: right;">Page 130</p> <p>1 Q. And -- and you understand 2 that's the first paragraph of -- under 3 the section Mandate and Methodology? 4 A. Under mandate it says, "I 5 was asked to review the scientific 6 literature and assess whether there is 7 biological plausible explanation for the 8 increased risk of ovarian cancer and the 9 perineal use of talcum powder products." 10 Q. And for purposes of your 11 mandate, did you assume that there was, 12 in fact, an increased risk of ovarian 13 cancer with the perineal use of talcum 14 powder? 15 A. I made no assumptions. 16 Q. Did you individually assess 17 whether there is an increased risk of 18 ovarian cancer with the perineal use of 19 talcum powder products? 20 A. Could you please slow down? 21 You are asking the question very quickly. 22 Q. Okay. Did you 23 individually -- did you do an analysis of 24 whether there's an increased risk of</p>	<p style="text-align: right;">Page 132</p> <p>1 Q. What graduate students 2 assisted you? 3 A. Are you asking me for their 4 names? 5 Q. Yes. 6 A. Nick Lawrence who was a 7 master student. And Catherine Fecchi who 8 was my master student. Both of them have 9 which graduated. 10 Q. Did you bill plaintiffs' 11 counsel for their time? 12 A. I paid them out of my 13 pocket. 14 Q. And how much did you pay 15 them per hour? 16 A. \$25 per hour. 17 Q. Do you describe -- strike 18 that. 19 Anyone else assist you with 20 your literature search? 21 A. I'm sorry, anyone else? 22 Q. Assist you in your 23 independent comprehensive literature 24 review.</p>
<p style="text-align: right;">Page 131</p> <p>1 ovarian cancer with perineal use of 2 talcum powder products? 3 A. No. As you can see by the 4 mandate I was asked to assess the 5 biological plausibility. I did no 6 analysis of causation. 7 Q. You did no analysis of 8 whether there is, in fact, an increased 9 risk of ovarian cancer with the perineal 10 use of talcum powder products? 11 A. I did no analysis of 12 causation. I'm not an epidemiologist. 13 Q. You also discuss in the 14 third paragraph, which begins "I 15 performed an independent comprehensive 16 literature review." 17 A. I see that, yes. Thank you. 18 Q. That you did do a literature 19 search, correct? 20 A. I did do a literature 21 search, correct. 22 Q. Did you do this yourself? 23 A. I did do this myself along 24 with several graduate students.</p>	<p style="text-align: right;">Page 133</p> <p>1 A. No, sir. 2 Q. So doing the searches was 3 part of your methodology for preparing 4 your report, correct? 5 A. Doing the searches were my 6 initial, my initial, yes. 7 Q. Did you prepare in advance a 8 written protocol on how you were going to 9 do the searches? 10 A. I followed the same protocol 11 that I used for papers, publications, 12 advisory boards, grant -- grant reviews 13 and grants that I write. 14 Q. That's not my question. My 15 question is, did you prepare a written 16 protocol as far as how you were going to 17 do the literature review for purposes of 18 your report? 19 A. I did not do a written 20 outline as to how to do this. I've been 21 doing this for over 35 years. 22 Q. You agree that it was part 23 of your methodology is -- for your 24 literature search, to find and review all</p>

<p style="text-align: right;">Page 134</p> <p>1 literature that touch on talc and its</p> <p>2 biologic effects, correct?</p> <p>3 MS. O'DELL: Object to the</p> <p>4 form.</p> <p>5 THE WITNESS: My purpose was</p> <p>6 to examine the literature, assess</p> <p>7 the literature, first identify the</p> <p>8 literature that I felt was --</p> <p>9 well, all -- all the literature</p> <p>10 that I could find or that the</p> <p>11 students could find, and from me</p> <p>12 to review them in terms of</p> <p>13 relevancy and pertinence to the</p> <p>14 question that I was being asked.</p> <p>15 BY MR. HEGARTY:</p> <p>16 Q. Did you do any testing of</p> <p>17 your methodology of doing searches to</p> <p>18 ensure that you had captured all the</p> <p>19 relevant literature?</p> <p>20 MS. O'DELL: Object to the</p> <p>21 form.</p> <p>22 THE WITNESS: What do you</p> <p>23 mean by testing?</p> <p>24 BY MR. HEGARTY:</p>	<p style="text-align: right;">Page 136</p> <p>1 reviewed all of the literature out</p> <p>2 there. I have no way of knowing</p> <p>3 that I reviewed or have not.</p> <p>4 I gathered the literature in</p> <p>5 a systematic fashion and I</p> <p>6 reviewed that literature.</p> <p>7 BY MR. HEGARTY:</p> <p>8 Q. Did you read every paper</p> <p>9 that you found from your literature</p> <p>10 search?</p> <p>11 A. Only those that were</p> <p>12 relevant. I read the abstracts to</p> <p>13 determine whether it was in fact related</p> <p>14 to the question that I was being asked.</p> <p>15 When you do a literature</p> <p>16 search, you come up with things that are</p> <p>17 related and some that are not related at</p> <p>18 all.</p> <p>19 Q. Does your report anywhere</p> <p>20 describe or include a description of how</p> <p>21 you weighed the various authorities that</p> <p>22 you reviewed?</p> <p>23 A. My report talks about under</p> <p>24 mandate and methodology how I -- the last</p>
<p style="text-align: right;">Page 135</p> <p>1 Q. Well, I don't know. Did you</p> <p>2 do any tests, having someone else do</p> <p>3 searches, repeating the searches, to see</p> <p>4 if your original searches captured all of</p> <p>5 the relevant literature?</p> <p>6 A. We did several searches</p> <p>7 doing -- using different words and</p> <p>8 different aspects, so that we could -- we</p> <p>9 got numerous duplicates because we came</p> <p>10 in with different words, and key --</p> <p>11 keywords and key phrases.</p> <p>12 Q. You do agree that it would</p> <p>13 be necessary for a proper methodology to</p> <p>14 reach opinions about biologic</p> <p>15 plausibility, that you have reviewed all</p> <p>16 the pertinent literature, correct?</p> <p>17 MS. O'DELL: Object to the</p> <p>18 form.</p> <p>19 THE WITNESS: To my</p> <p>20 knowledge I reviewed the</p> <p>21 literature that was pertinent to</p> <p>22 the question that I was being</p> <p>23 asked.</p> <p>24 I am not stating that I</p>	<p style="text-align: right;">Page 137</p> <p>1 paragraph, and that begins more than 300</p> <p>2 publications, will -- talks about how</p> <p>3 I -- how I looked at the publications and</p> <p>4 how I decided how to cut down or dismiss</p> <p>5 certain papers based on a closer</p> <p>6 scrutiny. And I focused specifically for</p> <p>7 biological plausibility and being a</p> <p>8 toxicologist on in vitro, in vivo, and ex</p> <p>9 vivo studies as well as cell studies,</p> <p>10 animal studies, and tissues.</p> <p>11 Q. Did you assign any numerical</p> <p>12 value to each authority as they relate to</p> <p>13 the importance to you?</p> <p>14 A. I did not assign any</p> <p>15 numerical value. There was no</p> <p>16 quantitative measurement done.</p> <p>17 Q. Was it also part of your</p> <p>18 methodology to review all expert reports</p> <p>19 in the litigation that concerned biologic</p> <p>20 plausibility?</p> <p>21 MS. O'DELL: Object to the</p> <p>22 form.</p> <p>23 THE WITNESS: Can you ask me</p> <p>24 that again, please.</p>

<p style="text-align: right;">Page 138</p> <p>1 BY MR. HEGARTY:</p> <p>2 Q. Sure. Was it part of your</p> <p>3 methodology to review all expert reports</p> <p>4 in the litigation concerning biologic</p> <p>5 plausibility?</p> <p>6 A. I -- I looked at reports</p> <p>7 that had relevancy in terms of animal</p> <p>8 models, in vitro cultures or ex vivo</p> <p>9 studies, yes. My opinion was formed</p> <p>10 primarily by the publications and the</p> <p>11 science that I reviewed.</p> <p>12 Q. Was it part of your</p> <p>13 methodology for purposes of your opinions</p> <p>14 to review the expert witness reports from</p> <p>15 the litigation that touch on biologic</p> <p>16 plausibility?</p> <p>17 MS. O'DELL: Object to the</p> <p>18 form. Asked and answered.</p> <p>19 THE WITNESS: I reviewed the</p> <p>20 publications and the book chapters</p> <p>21 and information that I thought</p> <p>22 would go towards my -- my opinion.</p> <p>23 BY MR. HEGARTY:</p> <p>24 Q. Your expert report, as we</p>	<p style="text-align: right;">Page 140</p> <p>1 THE WITNESS: To my</p> <p>2 knowledge, I have no knowledge as</p> <p>3 to how they selected the reports</p> <p>4 or which reports they selected to</p> <p>5 send.</p> <p>6 BY MR. HEGARTY:</p> <p>7 Q. You didn't have -- get a</p> <p>8 list of all expert reports and decide</p> <p>9 which ones you wanted, correct?</p> <p>10 MS. O'DELL: Object to the</p> <p>11 form.</p> <p>12 THE WITNESS: I -- no. I</p> <p>13 did not get a list of an entirety.</p> <p>14 BY MR. HEGARTY:</p> <p>15 Q. Do you know plaintiffs'</p> <p>16 counsel methodology for purposes of</p> <p>17 selecting the reports to provide to you?</p> <p>18 A. I do not know their</p> <p>19 methodology, but I would guess since</p> <p>20 papers were supplied to me that had both</p> <p>21 opinions and conclusions that led to</p> <p>22 either positive associations or lack of</p> <p>23 positive or data from scientific in vivo</p> <p>24 studies, et cetera, that showed effects</p>
<p style="text-align: right;">Page 139</p> <p>1 have looked at, includes references to</p> <p>2 several other experts' reports, correct?</p> <p>3 We looked at that earlier.</p> <p>4 A. If you say so, yes.</p> <p>5 Q. Did you select those expert</p> <p>6 reports for purposes of your review?</p> <p>7 MS. O'DELL: Object to the</p> <p>8 form.</p> <p>9 THE WITNESS: I formed my</p> <p>10 opinion with contributions from</p> <p>11 some of the reports that I had.</p> <p>12 But it was primarily based upon</p> <p>13 literature reviews.</p> <p>14 BY MR. HEGARTY:</p> <p>15 Q. The reports that you had</p> <p>16 were provided to you by plaintiffs'</p> <p>17 counsel, correct?</p> <p>18 A. Reports that I received was</p> <p>19 supplied to me by plaintiffs' counsel.</p> <p>20 Q. They selected the reports</p> <p>21 that they were going to provide to you,</p> <p>22 correct?</p> <p>23 MS. O'DELL: Object to the</p> <p>24 form.</p>	<p style="text-align: right;">Page 141</p> <p>1 and no effects, I would assume that I got</p> <p>2 all the literature both -- from both</p> <p>3 perceptions.</p> <p>4 Q. Can you identify any medical</p> <p>5 literature that you had reviewed prior to</p> <p>6 being contacted by Ms. Emmel?</p> <p>7 A. Medical literature on?</p> <p>8 Q. Let me finish my question.</p> <p>9 A. I'm sorry.</p> <p>10 Q. Can you identify any</p> <p>11 scientific or medical literature that you</p> <p>12 reviewed before being contacted by</p> <p>13 Ms. Emmel concerning talc and ovarian</p> <p>14 cancer?</p> <p>15 A. There is no literature that</p> <p>16 I reviewed prior to me being contacted by</p> <p>17 Ms. Emmel.</p> <p>18 Q. Also in Exhibit B --</p> <p>19 A. B as in boy?</p> <p>20 Q. -- boy -- to your report.</p> <p>21 There is a listing of produced documents</p> <p>22 by Bates number.</p> <p>23 A. Correct. I see it,</p> <p>24 "materials and data considered."</p>

<p style="text-align: right;">Page 142</p> <p>1 Q. Did the plaintiffs' counsel 2 provide you with copies of those 3 documents? 4 A. I have not gone through 5 every paper in those multiple binders. I 6 would assume that many of them are in 7 there. 8 Q. That's not my question, 9 Doctor. My question was, were those 10 documents provided to you by counsel for 11 plaintiffs? 12 MS. O'DELL: What documents 13 are you referring to? 14 MR. HEGARTY: The documents 15 that are listed by Bates number in 16 Exhibit B. 17 THE WITNESS: Oh, you're 18 talking about produced documents? 19 BY MR. HEGARTY: 20 Q. Yes. 21 A. Repeat your question, 22 please. 23 Q. Sure. Were the documents 24 listed by Bates number under produced</p>	<p style="text-align: right;">Page 144</p> <p>1 section "produced documents"? 2 A. I reviewed all of the 3 documents that are in the binder listed 4 as production documents. I did not check 5 one for another, so I cannot say I did 6 all of these -- 7 Q. Did you receive -- 8 A. -- or they did not. 9 Q. I'm sorry. Did you receive 10 from counsel from plaintiffs all the 11 documents that have been produced in this 12 litigation that concerned biologic 13 plausibility? 14 MS. O'DELL: Object to the 15 form. 16 THE WITNESS: I have no 17 knowledge of whether I received 18 every single document there is out 19 there. 20 BY MR. HEGARTY: 21 Q. Did you ask for -- did you 22 ask counsel for plaintiffs to provide you 23 all the documents that have been produced 24 in this case concerning biologic</p>
<p style="text-align: right;">Page 143</p> <p>1 documents provided to you by counsel for 2 plaintiffs? 3 A. Produced documents were 4 supplied to me in the folder that is 5 listed, production documents. 6 Q. Did you ask for those 7 specific documents? 8 A. I did not. 9 Q. Do you know what the 10 methodology was for selecting those 11 specific documents to send to you? 12 A. I do not. 13 MS. O'DELL: Object to the 14 form. 15 THE WITNESS: Sorry. 16 BY MR. HEGARTY: 17 Q. Did you ask for any 18 additional documents that would fall 19 under the definition of produced 20 documents besides those plaintiffs' 21 counsel provided to you? 22 A. Not to my knowledge. 23 Q. Did you review all the 24 documents that are listed under the</p>	<p style="text-align: right;">Page 145</p> <p>1 plausibility? 2 MS. O'DELL: Object to the 3 form. 4 THE WITNESS: Did not ask it 5 in that manner. 6 I did ask for in vitro 7 studies that they could find, ex 8 vivo studies, and I also did my 9 own literature search. Yes. 10 BY MR. HEGARTY: 11 Q. Were you -- did you 12 understand that -- or do you understand 13 that you've been provided with all the 14 produced documents that concern biologic 15 plausibility? 16 MS. O'DELL: Object to form. 17 THE WITNESS: I have no 18 knowledge of whether I received 19 all documents. 20 BY MR. HEGARTY: 21 Q. With regard to the produced 22 documents, did you sign a protective 23 order before reviewing those documents? 24 A. Regarding these produced</p>

<p style="text-align: right;">Page 146</p> <p>1 documents --</p> <p>2 Q. Yes.</p> <p>3 A. -- did I sign a protective</p> <p>4 order?</p> <p>5 Q. Yes.</p> <p>6 MS. O'DELL: Object to the</p> <p>7 form. It's a confidentiality</p> <p>8 order in this litigation. You may</p> <p>9 not be aware of it.</p> <p>10 MR. HEGARTY: Okay, well,</p> <p>11 confidentiality order.</p> <p>12 MS. O'DELL: Just so it's</p> <p>13 not unclear to the witness.</p> <p>14 BY MR. HEGARTY:</p> <p>15 Q. Did you sign a</p> <p>16 confidentiality order before reviewing</p> <p>17 the Bates-stamped documents?</p> <p>18 A. I signed a confidentiality</p> <p>19 agreement early on.</p> <p>20 Q. Do you rely on any tests for</p> <p>21 purposes of your opinions that are not</p> <p>22 reported in the medical literature?</p> <p>23 A. Again --</p> <p>24 MS. O'DELL: Object to the</p>	<p style="text-align: right;">Page 148</p> <p>1 experiments that I'm aware of that</p> <p>2 were done that I have knowledge</p> <p>3 of? No I have no knowledge of any</p> <p>4 laboratory testing or experimental</p> <p>5 testing in this field.</p> <p>6 BY MR. HEGARTY:</p> <p>7 Q. You did not do any testing</p> <p>8 yourself for purposes of developing your</p> <p>9 opinions in this case, correct?</p> <p>10 A. I did not do any laboratory</p> <p>11 tests.</p> <p>12 Q. All the opinions that are</p> <p>13 set out in your report about biologic</p> <p>14 plausibility between talc and ovarian</p> <p>15 cancer were formed after being contacted</p> <p>16 by counsel for plaintiffs about</p> <p>17 testifying as an expert in this case,</p> <p>18 correct?</p> <p>19 MS. O'DELL: Objection to</p> <p>20 form.</p> <p>21 THE WITNESS: After being</p> <p>22 contacted by the plaintiffs I did</p> <p>23 a literature search and followed</p> <p>24 the science.</p>
<p style="text-align: right;">Page 147</p> <p>1 form.</p> <p>2 THE WITNESS: Please</p> <p>3 describe "tests."</p> <p>4 BY MR. HEGARTY:</p> <p>5 Q. Well, did you rely on any</p> <p>6 testing or tests for purposes of your</p> <p>7 opinions that are not contained in the</p> <p>8 medical literature --</p> <p>9 MS. O'DELL: Objection to</p> <p>10 form.</p> <p>11 BY MR. HEGARTY:</p> <p>12 Q. -- that we wouldn't have</p> <p>13 access to but that you did?</p> <p>14 MS. O'DELL: Object to the</p> <p>15 form. Besides those produced in</p> <p>16 the litigation?</p> <p>17 MR. HEGARTY: Yeah, that</p> <p>18 goes without saying.</p> <p>19 MS. O'DELL: It doesn't go</p> <p>20 without saying. It's an unfair</p> <p>21 question.</p> <p>22 THE WITNESS: So if I</p> <p>23 understand your question to mean</p> <p>24 are there any laboratory</p>	<p style="text-align: right;">Page 149</p> <p>1 BY MR. HEGARTY:</p> <p>2 Q. That's not my question,</p> <p>3 Doctor.</p> <p>4 My question is, all the</p> <p>5 opinions set out in your report about</p> <p>6 biologic plausibility as they relate to</p> <p>7 talc and ovarian cancer were formed after</p> <p>8 being contacted by counsel for</p> <p>9 plaintiffs, correct?</p> <p>10 A. That is correct.</p> <p>11 Q. Can you cite for us any</p> <p>12 occasion where you've done the exact same</p> <p>13 thing that you have done here to prepare</p> <p>14 your report; that is, do an analysis of</p> <p>15 the literature on the biologic</p> <p>16 plausibility between the exposure to a</p> <p>17 substance and a disease?</p> <p>18 A. Nothing has been done</p> <p>19 exactly like it's been here, but for</p> <p>20 advisory boards that I've been on,</p> <p>21 including the National Toxicology Board,</p> <p>22 the Institute of Medicine, the Institute</p> <p>23 of Engineering for the National Academies</p> <p>24 of Science, we have -- we were requested</p>

<p style="text-align: right;">Page 150</p> <p>1 to do literature reviews on the question 2 that's in front of them and come up with 3 an opinion based upon our literature 4 reviews. 5 Q. Have you ever published an 6 article in the medical literature where 7 you've done the same thing that you've 8 done here, which is to review all the 9 literature on a substance and a disease 10 and offer opinions as to whether there's 11 biologic plausibility between that 12 substance and a disease? 13 A. I have written reviews that 14 are a culmination of all of the 15 literature that I reviewed on topics. 16 Never one on ovarian cancer and talc. 17 And to my knowledge, I have 18 not offered an opinion, but followed a 19 conclusion from the science. 20 Q. I think my question is a 21 little bit different. My question is, 22 have you published any article in the 23 literature where you have done 24 essentially the same thing that you have</p>	<p style="text-align: right;">Page 152</p> <p>1 the words "biological feasibility" or 2 "potential mechanisms" or "plausible" -- 3 I may have used the word "plausibility," 4 but I have used words that are similar to 5 those. 6 Q. Doctor, when did you first 7 become aware of an alleged link between 8 ovarian cancer and talc use? 9 MS. O'DELL: Object to the 10 form. 11 THE WITNESS: When did I 12 first become aware of the alleged 13 link between ovarian cancer and 14 talc use? From -- from the media. 15 I would say maybe a year prior to 16 being contacted by Ms. Emmel. 17 BY MR. HEGARTY: 18 Q. Can you cite for me any 19 scientific or medical group, entity or 20 organization who has concluded that 21 genital talc use causes ovarian cancer? 22 A. I -- really, my opinion is 23 based on biological plausibility. 24 Q. I understand that. But my</p>
<p style="text-align: right;">Page 151</p> <p>1 done here, which is review all the 2 literature on an exposure and a disease 3 and offer opinions as to whether there's 4 biologic plausibility between the 5 exposure and the disease? 6 A. Most of the papers that I 7 publish will offer a potential, whether a 8 speculative potential or one that is 9 defined within other published literature 10 as a potential mechanism of action or as 11 potential plausible outcome. 12 So for any published paper 13 from the research that I've done or that 14 people do, we explain an observation that 15 has been found in our laboratory from 16 testing, as you call it. And we will 17 explain the observation in terms of 18 biological plausibility, if that's what 19 you're referring to. 20 Q. Well, have you ever used the 21 phrase "biologic plausibility" in any 22 published article? 23 A. I cannot cite them for you, 24 but I -- I am confident that I have used</p>	<p style="text-align: right;">Page 153</p> <p>1 question is simply from your knowledge, 2 here today, can you cite for me any 3 scientific or medical group, entity or 4 organization who has concluded that 5 genital talc use causes ovarian cancer? 6 MS. O'DELL: Object to the 7 form. 8 THE WITNESS: Well, 9 concluded is -- is a word for 10 discussion. 11 IARC in the 1993 report from 12 inhalation toxicology and 13 inhalation of talc did show that 14 there was tumor induction in 15 female rats in the lungs and that 16 there was adrenal gland tumors 17 that were formed. 18 BY MR. HEGARTY: 19 Q. Well, IARC has never 20 concluded that the use of talc in the 21 genital area causes ovarian cancer, 22 correct? 23 A. You asked me whether there 24 was any body of literature or any</p>

<p style="text-align: right;">Page 154</p> <p>1 advisory boards or any institution which 2 has concluded that there is a causal 3 relationship. And I've cited to you a 4 study -- 5 Q. That's not my question. My 6 question was can you cite for me any 7 scientific or medical group, entity or 8 organization who has concluded that 9 genital talc use causes ovarian cancer. 10 MS. O'DELL: Object to the 11 form. 12 THE WITNESS: I have -- I 13 have given you information on a 14 study done at the national 15 toxicology program. 16 BY MR. HEGARTY: 17 Q. Is that the extent of your 18 answer? 19 A. There are -- to my 20 knowledge, that's the best study that I 21 can cite to you. 22 Q. That's a study, correct? 23 A. That was a study, and they 24 are also a body that makes conclusions.</p>	<p style="text-align: right;">Page 156</p> <p>1 BY MR. HEGARTY: 2 Q. II-B is possibly 3 carcinogenic, correct? 4 A. To humans. 5 Q. I'm sorry? 6 A. To humans. Possibly 7 carcinogenic to humans. That doesn't 8 exclude the fact that there is animal 9 data supporting that conclusion. If 10 there were no animal data it -- it would 11 not even be considered a II-B. So 12 there -- there's evidence that the IARC 13 evaluated and came up with a II-B 14 classification. 15 Q. Is it your opinion that the 16 biologic plausibility of talc products 17 causing ovarian cancer has been generally 18 accepted in the medical community? 19 A. I think it depends on the 20 medical community. 21 Q. Well, aside from any medical 22 community that has accepted that there is 23 biologic plausibility between the use of 24 talc products in -- in ovarian cancer.</p>
<p style="text-align: right;">Page 155</p> <p>1 Q. That study did not involve 2 any commentary on ovarian cancer, 3 correct? 4 A. The study did not involve 5 commentary on that. 6 Q. Can you name any regulatory 7 body who has stated that talc use is a 8 cause of ovarian cancer? 9 A. Not as I sit here right now. 10 But again, making conclusions on 11 causation was not my question, is not 12 my -- is not within my purview. 13 And there are different 14 levels of cancer conclusion. For 15 instance, IARC has several 16 classifications. And -- as you know, I, 17 II-A, II-B, et cetera. 18 Q. And what is IARC's 19 classification of talc use in the genital 20 area? 21 MS. O'DELL: Object to the 22 form. 23 THE WITNESS: To my 24 knowledge, I think it's a II-B.</p>	<p style="text-align: right;">Page 157</p> <p>1 Let me -- let me restate that. 2 Can you cite for me any 3 medical community that has accepted that 4 there is biologic plausibility of talc 5 products causing ovarian cancer? 6 A. I'm not knowledgeable at -- 7 about all the medical communities and 8 what disciplines they are in. 9 Q. Well, can you cite for me 10 any medical or scientific community that 11 has accepted that there is biologic 12 plausibility of talcum powder products 13 causing ovarian cancer? 14 A. I have no knowledge of that. 15 That doesn't mean it's not out there. It 16 means that I have no knowledge of that. 17 Q. You have no knowledge -- 18 you -- so you cannot testify that the 19 medical or scientific communities have 20 accepted that there is biologic 21 plausibility of talcum powder products 22 causing ovarian cancer? 23 MS. O'DELL: Object to the 24 form.</p>

<p style="text-align: right;">Page 158</p> <p>1 THE WITNESS: What I'm</p> <p>2 saying is I have no knowledge of</p> <p>3 the documents they have put out</p> <p>4 with a conclusion as a white paper</p> <p>5 or any other published literature</p> <p>6 that has made that conclusion.</p> <p>7 BY MR. HEGARTY:</p> <p>8 Q. What does -- sorry.</p> <p>9 A. Or has not made that</p> <p>10 conclusion.</p> <p>11 Q. What does general acceptance</p> <p>12 mean to you?</p> <p>13 A. General acceptance -- for</p> <p>14 example, benzene, it causes leukemia and</p> <p>15 other blood cancers. That is a general</p> <p>16 acceptance by the medical community which</p> <p>17 we all adhere to, abide by, based upon</p> <p>18 the excessive amount of literature that</p> <p>19 is out there showing -- proving and</p> <p>20 addressing Hill's criteria and coming up</p> <p>21 with the fact that it is a -- it is a</p> <p>22 carcinogen for blood cancers.</p> <p>23 That is general knowledge.</p> <p>24 General knowledge is something saying</p>	<p style="text-align: right;">Page 160</p> <p>1 Thank you.</p> <p>2 BY MR. HEGARTY:</p> <p>3 Q. You don't -- you don't know</p> <p>4 what a cosmetic is?</p> <p>5 A. I'm asking you what your</p> <p>6 definition is.</p> <p>7 Q. Well, I -- what is your</p> <p>8 definition?</p> <p>9 A. A definition of a cosmetic</p> <p>10 is -- since I'm not in the cosmetic</p> <p>11 field -- a cosmetic is something that is</p> <p>12 used for hygiene or aesthetics and used</p> <p>13 dermally.</p> <p>14 Q. Have you ever written any</p> <p>15 scientific article about a cosmetic under</p> <p>16 your definition?</p> <p>17 A. Not to my knowledge, but I</p> <p>18 would have to look at all of my papers</p> <p>19 again, if you'd like me to do that.</p> <p>20 Q. Can you cite for me any</p> <p>21 publication of yours where you comment on</p> <p>22 asbestos?</p> <p>23 A. I would have to look at my</p> <p>24 references. I go back from 1982.</p>
<p style="text-align: right;">Page 159</p> <p>1 that nickel can be a carcinogen, nickel</p> <p>2 is a carcinogen and is classified by IARC</p> <p>3 as a I. In that case, the general</p> <p>4 population is aware of that.</p> <p>5 Q. Before being hired by the</p> <p>6 plaintiffs' lawyers in this case, you had</p> <p>7 never written anything about talc,</p> <p>8 correct?</p> <p>9 A. That's correct.</p> <p>10 Q. Or commented on talc in any</p> <p>11 setting, correct?</p> <p>12 A. Other than teaching?</p> <p>13 Q. Other than the teaching</p> <p>14 reference you cited earlier?</p> <p>15 A. That's correct.</p> <p>16 Q. Before being hired by</p> <p>17 plaintiffs' counsel you had never written</p> <p>18 anything about any cosmetic, correct?</p> <p>19 MS. O'DELL: Object to the</p> <p>20 form.</p> <p>21 Could you please -- it's</p> <p>22 vague in terms of cosmetic. Do</p> <p>23 you have a definition in mind?</p> <p>24 THE WITNESS: Exactly.</p>	<p style="text-align: right;">Page 161</p> <p>1 Q. Sitting here today, can you</p> <p>2 cite for us, without looking at any</p> <p>3 references, any article you've ever</p> <p>4 written about asbestos?</p> <p>5 MS. O'DELL: Doctor, if you</p> <p>6 need to look at your CV, you're</p> <p>7 welcome to do that.</p> <p>8 BY MR. HEGARTY:</p> <p>9 Q. Well, my question didn't ask</p> <p>10 about the CV. I said just simply sitting</p> <p>11 here today, just based on your memory --</p> <p>12 A. Okay.</p> <p>13 Q. -- are you able to recall</p> <p>14 any article you've ever written about</p> <p>15 asbestos.</p> <p>16 MS. O'DELL: If you would</p> <p>17 like to look at your CV, it's in</p> <p>18 front of you. You are welcome</p> <p>19 to -- to do that.</p> <p>20 MR. HEGARTY: I'll withdraw</p> <p>21 the question.</p> <p>22 BY MR. HEGARTY:</p> <p>23 Q. Doctor, have you ever</p> <p>24 written any article about a fragrance?</p>

<p style="text-align: right;">Page 162</p> <p>1 A. I would also like to look at 2 my CV. 3 Q. Without looking at your CV, 4 you can't say one way or the other? 5 A. I can't say conclusively. 6 My CV and my publications go back to 7 1982. It was quite a while ago. 8 Q. And you can't say 9 conclusively whether you've written an 10 article about asbestos? 11 A. I would rather look at my -- 12 my publications. 13 Q. Okay. Have you ever 14 written -- 15 A. Would you like me to do 16 that, sir? 17 Q. No. I'm not asking you to 18 do that right now. 19 A. Thank you. 20 Q. Sitting here today without 21 looking at your CV, can you cite for me 22 any article you've ever written about 23 asbestos? 24 MS. O'DELL: Objection to</p>	<p style="text-align: right;">Page 164</p> <p>1 as scientists, involved as co-authors, 2 oftentimes. And I do not recall back to 3 1982. 4 Q. Well, for purposes of your 5 report, you do not cite to any of your 6 own work, correct? 7 A. That is correct. 8 Q. You've never written 9 anything about talc and ovarian cancer, 10 correct? 11 A. I think I asked and answered 12 that. I think I answered that. But I 13 can repeat it. 14 Q. No, you did not. I did not 15 ask you that question, ma'am. 16 A. So can -- 17 Q. I asked you had you ever 18 written anything about talc. My question 19 that I just asked you is have you ever 20 written anything about talc and ovarian 21 cancer? 22 A. To my knowledge, as I sit 23 here now without looking at my 24 publications, no.</p>
<p style="text-align: right;">Page 163</p> <p>1 form. 2 THE WITNESS: To my 3 knowledge at this particular 4 moment, I cannot cite for you an 5 article that I specifically wrote 6 on asbestos. Whether or not I was 7 a co-author on one, I cannot 8 recall. 9 BY MR. HEGARTY: 10 Q. Would that be the same 11 answer as to a fragrance? 12 A. I -- I would really rather 13 look at my CV and my publications and 14 book chapters. 15 Q. Before being contacted by 16 counsel for plaintiffs in this case, you 17 had never developed or offered any 18 opinions about talc, correct? 19 A. That is correct. 20 Q. You've never written 21 anything about ovarian cancer, correct? 22 A. Again, just to put on the 23 record, I would really like to look at my 24 CV and look at my publications. We are,</p>	<p style="text-align: right;">Page 165</p> <p>1 Q. Prior to being contacted by 2 plaintiff's counsel have you ever 3 reviewed the body of literature on the 4 etiologies or biology related to ovarian 5 cancer? 6 A. Not prior to being 7 contacted, no. 8 Q. You've never published any 9 opinions about the causes of ovarian 10 cancer, correct? 11 A. To my knowledge, sitting 12 here, no. 13 Q. You never published any 14 opinions about the risk factors for 15 ovarian cancer, correct? 16 A. I really -- I'm not sure. I 17 know that I have given that information, 18 not an opinion, but have given that 19 information in teaching courses. 20 Q. Have you ever taught any 21 courses on asbestos? 22 A. Asbestos has been included. 23 I give lectures in my organ system 24 toxicology course as well as in my</p>

<p style="text-align: right;">Page 166</p> <p>1 toxicology course for biology masters. I 2 give courses in air pollutants and 3 cancer-causing agents and the toxicology 4 of -- of airborne. 5 Q. Have you ever taught in your 6 courses any discussion about fragrances 7 and toxicity? 8 A. It may have come up as a 9 minor point. We talk about pesticides, 10 we talk about air pollutants. We talk 11 about metals. Fragrances, we talked 12 about limonene, eugenol, menthol and 13 other fragrances in that realm in the 14 discussion of electronic cigarettes and 15 the aerosols produced by them. 16 Q. And you provided to us all 17 the lectures or the content of lectures 18 that you've given where you mentioned 19 talc, correct? 20 A. I was not asked to -- 21 MS. O'DELL: Object to the 22 form. 23 THE WITNESS: I was not 24 asked to provide them. But please</p>	<p style="text-align: right;">Page 168</p> <p>1 reproductive docs who do focus on this, 2 yes. 3 Q. And that has not been an 4 area of your focus, correct? 5 A. Not -- not in past. Has not 6 been a primary focus. 7 Q. You have provided for us 8 your CV, correct? 9 A. That is correct. 10 Q. That's included as part of 11 Exhibit B to your expert report, correct? 12 MS. O'DELL: Objection to 13 form. 14 THE WITNESS: I think it's 15 stated here as Exhibit A. 16 BY MR. HEGARTY: 17 Q. It's Exhibit A to your 18 expert report. Is that a current CV of 19 yours? 20 A. It was updated in 21 August 2018. So it is not completely 22 updated as of January 2019. 23 Q. Did you bring an updated CV 24 to your deposition?</p>
<p style="text-align: right;">Page 167</p> <p>1 let me explain my teaching style. 2 My teaching style is such 3 that I use few PowerPoints as 4 queues. And much of my teaching 5 is done verbally, one-on-one. And 6 they're not recorded. 7 So there is really not that 8 much -- there is nothing to supply 9 to counsel. 10 BY MR. HEGARTY: 11 Q. Well, other than the 12 reference that you provided to us earlier 13 about talc and ovarian cancer, you have 14 not otherwise lectured regarding this 15 subject, correct? 16 A. That is correct. 17 Q. There are toxicologists who 18 focus on issues dealing with reproductive 19 medicine or reproductive sciences such as 20 ovarian cancer and uterine cancer, 21 correct? 22 A. There are scientists whose 23 major focus is on talc and ovarian cancer 24 and there are OB/GYNs as well as</p>	<p style="text-align: right;">Page 169</p> <p>1 A. I did not. 2 Q. As you stated -- 3 A. I'm sorry. I can provide 4 that. 5 Q. Does your CV anywhere list 6 any professional experience on ovarian 7 cancer? 8 A. Excuse me. Not to my 9 knowledge, in briefly reviewing my CV, 10 and not to my knowledge as I sit here. 11 Q. Does your CV list any 12 professional experience regarding 13 asbestos? 14 A. Specifically, asbestos as I 15 review, no. No, sir. 16 Q. Does your CV list any 17 professional experience regarding 18 fragrances? 19 A. Not to my knowledge, no, 20 sir. But you're asking me only what's in 21 my CV. 22 I have -- I have worked -- I 23 have looked at or heard about from other 24 advisory boards things to do with</p>

<p style="text-align: right;">Page 170</p> <p>1 flavorants, as I said with electronic 2 cigarettes, hookah and smokeless tobacco. 3 So I am familiar with other -- which may 4 not be listed here in detail, which is 5 not listed here in detail, on flavorants 6 and some of those same flavors used in 7 electronic cigarettes are also, I found, 8 listed here.</p> <p>9 Q. Has any entity or agency 10 consulted you with regard to diseases of 11 the female reproductive tract?</p> <p>12 MS. O'DELL: Object to the 13 form.</p> <p>14 THE WITNESS: Not to my 15 knowledge.</p> <p>16 BY MR. HEGARTY:</p> <p>17 Q. And no one has ever asked 18 you to look into any of the issues set 19 out in your report besides plaintiffs' 20 counsel, correct?</p> <p>21 A. I'm sorry. Again?</p> <p>22 Q. No one has asked you to look 23 at the issues set out in your expert 24 report in this case other than</p>	<p style="text-align: right;">Page 172</p> <p>1 or scientist who believes that there is 2 biologic plausibility between use of 3 talcum powder and ovarian cancer?</p> <p>4 MS. O'DELL: Object to form.</p> <p>5 THE WITNESS: I have not 6 spoken to any doctors in that 7 regard.</p> <p>8 BY MR. HEGARTY:</p> <p>9 Q. How about any scientists?</p> <p>10 A. I have not spoke to any 11 scientists in that regard.</p> <p>12 Q. Have you --</p> <p>13 A. My opinion was specifically 14 based upon the scientific literature that 15 I had access to.</p> <p>16 Q. Have you ever had your 17 deposition taken before?</p> <p>18 A. I have. Yes, sir.</p> <p>19 Q. How many times?</p> <p>20 A. One that I can recall. Two 21 that I'm now recalling. One that was 22 in -- for Dow Chemical on breast implants 23 and relationship with autoimmune disease 24 and one from a personal attorney who</p>
<p style="text-align: right;">Page 171</p> <p>1 plaintiffs' counsel, correct?</p> <p>2 A. This specific ovarian cancer 3 and asbestos, that is correct.</p> <p>4 Q. You have not submitted your 5 expert report in this case for peer 6 review, correct?</p> <p>7 A. The only ones who have seen 8 my report have been the plaintiff 9 attorneys, to my knowledge.</p> <p>10 If that was given out to 11 others at that point, I do not -- I do 12 not have knowledge of that.</p> <p>13 Q. You certainly have not 14 submitted your report for peer review, 15 correct?</p> <p>16 A. I have not submitted my 17 report for peer review.</p> <p>18 Q. Have you spoken to any 19 physicians who treat ovarian cancer 20 regarding talc and ovarian cancer?</p> <p>21 A. I have not.</p> <p>22 Q. Other than experts 23 identified by plaintiffs in this 24 litigation, can you identify any doctor</p>	<p style="text-align: right;">Page 173</p> <p>1 was -- who had a client who was exposed 2 to wood burning from a wood stove, an 3 outdoor wood stove.</p> <p>4 Q. As to the latter case, do 5 you know where that case was pending or 6 was filed?</p> <p>7 A. I was deposed in New York 8 City.</p> <p>9 Q. Do you know the name of the 10 case?</p> <p>11 A. I'm afraid not, sir.</p> <p>12 Q. How long ago was it?</p> <p>13 A. 15 years.</p> <p>14 Q. You were testifying on 15 behalf of the plaintiff in that case?</p> <p>16 MS. O'DELL: Object to form.</p> <p>17 THE WITNESS: I was not 18 testifying. I was deposed for 19 the -- sorry, for the person who 20 was making the claim that they had 21 increased asthma as a result of 22 neighbors use of a wood boiler.</p> <p>23 BY MR. HEGARTY:</p> <p>24 Q. In the Dow Chemical breast</p>

<p style="text-align: right;">Page 174</p> <p>1 implant case, were you testifying as an 2 expert witness? 3 A. I was. 4 Q. On behalf of the plaintiffs? 5 A. If you're talking about on 6 the part of Dow, yes. 7 Q. Well, on the part of Dow who 8 was the defendant or the plaintiffs? 9 A. Dow was the defendant. I'm 10 sorry. 11 Q. Were you testifying on 12 behalf of Dow? 13 A. I was. 14 Q. Any other cases you've been 15 deposed in? 16 A. Not that I can recall. 17 Q. Have you been identified in 18 any other cases as an expert witness 19 besides this one to your knowledge? 20 A. I have done literature 21 reviews for a number of attorneys but 22 have not been deposed. 23 Q. My question is specific to 24 whether you -- whether you are aware that</p>	<p style="text-align: right;">Page 176</p> <p>1 cases -- are there any articles on which 2 you rely for purposes of your opinions -- 3 strike that. Let me ask it a different 4 way. 5 How many articles have you 6 published since August of 2018? 7 A. I'm going to look at the 8 last publication. 9 I have one that was accepted 10 in press on the Garfield community and 11 looking at chromium exposure and doing 12 community engagement for the community 13 and looking at blood level of 14 measurements -- or toenail measurements, 15 excuse me, toenail measurement of 16 chromium, as they're impacting 17 communities environmentally. 18 Also two publications have 19 come out with the lead author, my being a 20 corresponding author with the lead author 21 being from the University of Rochester in 22 the area of inhaled particulate matter 23 and -- during pregnancy and effects on 24 the -- on the offspring and on the fetus.</p>
<p style="text-align: right;">Page 175</p> <p>1 you've been designated, identified, in 2 the case as a testifying expert besides 3 this case. Are you aware of any such 4 cases? 5 A. Not to my knowledge. 6 Q. I know I referred earlier to 7 your CV. But I'm marking it as 8 Exhibit 22. You can look at that one or 9 Exhibit 22. 10 (Document marked for 11 identification as Exhibit 12 Zelikoff-22.) 13 BY MR. HEGARTY: 14 Q. Are there any publications 15 of yours that relate to any of the issues 16 in this case that are not included in 17 your CV? 18 MS. O'DELL: Object to form. 19 THE WITNESS: Let's talk 20 about the issues of the case. Can 21 you define them a little better? 22 BY MR. HEGARTY: 23 Q. Yeah, let me ask you a 24 different question. Are there any</p>	<p style="text-align: right;">Page 177</p> <p>1 Q. You are not a medical 2 doctor, correct? 3 A. I am not a medical doctor, 4 although I did go to medical school for 5 my Ph.D. training. 6 Q. You can't treat patients, 7 correct? 8 A. I do not treat patients. 9 Q. You are not an oncologist, 10 correct? 11 A. I am not an oncologist. 12 Q. You have no training in 13 oncology, correct? 14 A. I have no training in 15 oncology. I have training in pathology, 16 which is what I got my Ph.D. degree in at 17 a medical school. 18 Q. You have never diagnosed or 19 treated a disease in a patient, including 20 cancer, correct? 21 A. That is correct. 22 Q. You have no expertise in 23 treating patients with ovarian cancer, 24 correct?</p>

<p style="text-align: right;">Page 178</p> <p>1 A. I have no expertise in that,</p> <p>2 no.</p> <p>3 Q. You have no expertise in</p> <p>4 diagnosing ovarian cancer, correct?</p> <p>5 A. I do not.</p> <p>6 Q. You are not an expert on</p> <p>7 asbestos, correct?</p> <p>8 A. I have not been classified</p> <p>9 as an expert in asbestos, although as I</p> <p>10 said, I do work in air pollution and if</p> <p>11 asbestos is in the confines -- taken in</p> <p>12 the confines of air pollution, I could</p> <p>13 speak to that. But I have not been</p> <p>14 designated as an expert.</p> <p>15 Q. What's the difference</p> <p>16 between amphibole and serpentine forms of</p> <p>17 asbestos?</p> <p>18 MS. O'DELL: Object to form.</p> <p>19 BY MR. HEGARTY:</p> <p>20 Q. You can answer.</p> <p>21 A. It depends on whether it's</p> <p>22 asbestiform or non-asbestiform.</p> <p>23 Q. Okay. Asbestiform. What's</p> <p>24 the difference between amphibole and</p>	<p style="text-align: right;">Page 180</p> <p>1 those forms can exist both in</p> <p>2 crystalline form or in a</p> <p>3 non-asbestiform.</p> <p>4 So they are both -- both</p> <p>5 concluded to be asbestos.</p> <p>6 BY MR. HEGARTY:</p> <p>7 Q. Well, are there any</p> <p>8 differences between --</p> <p>9 A. By the EPA.</p> <p>10 Q. Are there any differences</p> <p>11 between amphibole and serpentine forms of</p> <p>12 asbestos?</p> <p>13 MS. O'DELL: Object to form.</p> <p>14 THE WITNESS: Well, they are</p> <p>15 different -- they are different</p> <p>16 minerals. But they are both</p> <p>17 classified as asbestos.</p> <p>18 BY MR. HEGARTY:</p> <p>19 Q. Any other differences?</p> <p>20 A. It -- both of which contain</p> <p>21 carcinogenic -- classified I, as IARC.</p> <p>22 Both have within them carcinogenic</p> <p>23 asbestos. To my knowledge, that is --</p> <p>24 that is all I --</p>
<p style="text-align: right;">Page 179</p> <p>1 serpentine forms?</p> <p>2 A. Well --</p> <p>3 MS. O'DELL: Object to the</p> <p>4 form.</p> <p>5 THE WITNESS: Amphibole</p> <p>6 lists serpentine which is</p> <p>7 associated with chrysotile. They</p> <p>8 all have an aspect ratio of,</p> <p>9 depending on who you are looking</p> <p>10 at, whether it's three to one or</p> <p>11 five to one. Johnson & Johnson</p> <p>12 includes it as five to one, which</p> <p>13 is length-to-width ratio. They</p> <p>14 both have the same length-to-width</p> <p>15 ratio.</p> <p>16 If they're asbestiform, then</p> <p>17 they are fibers that are made up</p> <p>18 of fibrils. They both have that.</p> <p>19 And they go in a</p> <p>20 longitudinal manner and they are</p> <p>21 in one direction.</p> <p>22 Amphibole includes within it</p> <p>23 the crocidolite, and as well as</p> <p>24 tremolite, amosite, and some of</p>	<p style="text-align: right;">Page 181</p> <p>1 Q. What was the most</p> <p>2 commercially used asbestos?</p> <p>3 A. Well, it -- it depends on</p> <p>4 the time. But for commercial use, in</p> <p>5 paints and housing and insulation, it was</p> <p>6 either chrysotile was used commercially</p> <p>7 and crocidolite was also used</p> <p>8 commercially.</p> <p>9 Q. Okay. How did the supposed</p> <p>10 toxicities various -- vary across the</p> <p>11 various forms of asbestos?</p> <p>12 MS. O'DELL: Object to the</p> <p>13 form.</p> <p>14 THE WITNESS: When you say</p> <p>15 toxicity what do you mean?</p> <p>16 BY MR. HEGARTY:</p> <p>17 Q. The -- the toxicities vary</p> <p>18 across the various forms.</p> <p>19 MS. O'DELL: Object to the</p> <p>20 form.</p> <p>21 THE WITNESS: Mm-hmm. It</p> <p>22 depends on the chemical</p> <p>23 composition. It depends on the</p> <p>24 surface material. It depends on</p>

<p style="text-align: right;">Page 182</p> <p>1 the amount of iron. It depends on 2 the size of the fiber or the 3 crystal. 4 And so depending upon those 5 factors you are going to have 6 differences in toxicity. 7 BY MR. HEGARTY: 8 Q. Well, how does -- does 9 tremolite asbestos compare to chrysotile 10 asbestos in terms of toxicity? 11 A. I don't really -- I don't 12 think I can answer that in terms of 13 ranking it. I can tell you that 14 chrysotile is a well-known carcinogen, 15 well-established carcinogen by the 16 agencies. That tremolite is an amphibole 17 and it can exist in both forms, either 18 asbestiform in the long longitudinal 19 fibriles, or it can exist as a mineral 20 that has dimensions in all different 21 directions. 22 So tremolite -- it's 23 difficult to rank, but chrysotile appears 24 to be -- when you say more toxic, you</p>	<p style="text-align: right;">Page 184</p> <p>1 Q. You are not an expert in 2 fragrances, correct? 3 MS. O'DELL: Object to form. 4 THE WITNESS: I have -- I 5 have not been listed as an expert 6 in fragrances. 7 BY MR. HEGARTY: 8 Q. Would you consider yourself 9 an expert in fragrances? 10 A. I am a toxicologist so I can 11 review chemicals and make a decision or 12 assess their toxicity based on outcomes. 13 Q. Before being contacted by 14 Ms. Emmel in this case, would you have 15 considered yourself an expert in 16 fragrances? 17 MS. O'DELL: Objection. 18 THE WITNESS: Expert in 19 fragrances. It is not something I 20 studied in my own laboratory. 21 However, a toxicologist 22 should be able to go into the 23 literature and have a greater 24 knowledge than most people in</p>
<p style="text-align: right;">Page 183</p> <p>1 have to understand what is the outcome 2 that you're looking at. They can both 3 cause toxicity. I don't know what you 4 exactly mean by more toxic. 5 Do you mean at a given 6 dose -- what -- what do you mean by -- 7 Q. I didn't -- I didn't use the 8 word "more toxic." I just -- I asked you 9 how does tremolite asbestos compare to 10 chrysotile asbestos in terms of toxicity. 11 A. I think I -- yeah, that's a 12 very difficult question to a 13 toxicologist. Because when you compare 14 toxicity across -- across lines, you have 15 to somehow rank them based on a 16 particular outcome. 17 So toxicity could be does it 18 produce more lactate dehydrogenase when 19 put in a macrophages culture of -- of 20 pulmonary cells, or does it produce more 21 apoptosis. You can't just say toxicity 22 in my opinion. You have to give me an 23 outcome. Does this produce more toxicity 24 in this area.</p>	<p style="text-align: right;">Page 185</p> <p>1 looking up different chemicals. 2 BY MR. HEGARTY: 3 Q. You are not an expert on 4 talc, correct? 5 MS. O'DELL: Object to the 6 form. 7 THE WITNESS: I have done 8 much work in dust, including the 9 World Trade Center dust. I've 10 done work on diesel exhaust and 11 other things that are powders. So 12 particularly talc, I don't think I 13 am classified as a talc expert. 14 But as I said I've done much 15 work in other dusts, other 16 aerosols, vapors, gases, 17 particles, and I am an expert in 18 particles. 19 BY MR. HEGARTY: 20 Q. You are not a geneticist, 21 correct? 22 A. I'm -- if a geneticist is 23 someone who has been trained specifically 24 in genetics, I have not been trained in</p>

<p style="text-align: right;">Page 186</p> <p>1 genetics. I have had courses in 2 molecular toxicology and I do teach some 3 molecular toxicology. 4 Q. You are not a mineralogist, 5 correct? 6 A. I am not a mineralogist. 7 Q. You are not an expert on 8 testing for the presence of asbestos, 9 correct? 10 A. I am not a chemist. 11 Q. You are not an expert on 12 testing the air for asbestos, correct? 13 A. We collect -- I collect 14 particles in the air. I do air 15 measurements. That is the basis of my 16 research. 17 When it comes to asbestos, 18 we will send those -- those filters out 19 to be analyzed by an expert laboratory, 20 and then we will help interpret the data. 21 Q. You are not an industrial 22 hygienist, correct? 23 A. I work with industrial 24 hygienists, but I do not have a degree in</p>	<p style="text-align: right;">Page 188</p> <p>1 components by percentage of Johnson's 2 Baby Powder? 3 MS. O'DELL: Object to the 4 form. Vague. 5 THE WITNESS: I cannot -- 6 although I have looked at it, I 7 cannot tell you that off the top 8 of my head. I would have to 9 look -- refresh my memory by 10 looking at an exhibit or a 11 document. 12 BY MR. HEGARTY: 13 Q. What were the current 14 components of Johnson's Baby Powder by 15 percentage from the 19 -- 1900s through 16 the present? 17 A. I cannot -- 18 MS. O'DELL: Excuse me. 19 Excuse me. Object to the form. 20 Vague. 21 THE WITNESS: I cannot give 22 you percentages off the top of my 23 head. If you allow me to look at 24 a document I -- I could tell you.</p>
<p style="text-align: right;">Page 187</p> <p>1 it. 2 Q. You are not an expert on 3 Johnson's Baby Powder, correct? 4 MS. O'DELL: Objection to 5 form. 6 THE WITNESS: I am not an 7 expert on -- I -- could you 8 rephrase that? 9 BY MR. HEGARTY: 10 Q. I don't think I can. 11 A. I don't know what you mean 12 by expert. I mean I need to have -- I 13 think I need to have some criteria that 14 would make me an expert. If you are 15 talking about the number of publications 16 I have or whether I've testified. 17 I -- the word "expert" 18 throws me off a bit. 19 Q. Well, where is the talc for 20 J&J's Baby Powder been mined over the 21 years? 22 A. In Vermont, in Italy, and 23 also in Korea. 24 Q. What are the current</p>	<p style="text-align: right;">Page 189</p> <p>1 BY MR. HEGARTY: 2 Q. Are the opinions in your 3 report specific to particular 4 formulations of talcum powder consumer 5 products? 6 MS. O'DELL: Object to the 7 form. 8 THE WITNESS: Are the 9 opinions in your report specific 10 to particular formulations. 11 My opinion is based on 12 biological plausibility based on 13 studies that have used talcum 14 powder or talc or fibrous talc or 15 nonfibrous talc. 16 BY MR. HEGARTY: 17 Q. Did you analyze specifically 18 the biologic plausibility of the 19 components of Johnson's Baby Powder for 20 purposes of your opinions? 21 MS. O'DELL: Object to the 22 form. 23 THE WITNESS: I looked at 24 the individual components that I</p>

<p style="text-align: right;">Page 190</p> <p>1 was aware of. And looked at their</p> <p>2 ability to cause inflammation,</p> <p>3 let's say, or their carcinogenic</p> <p>4 potential.</p> <p>5 BY MR. HEGARTY:</p> <p>6 Q. But did you look</p> <p>7 specifically -- did you specifically</p> <p>8 analyze biologic plausibility specific to</p> <p>9 J&J's -- strike that.</p> <p>10 Did you analyze biological</p> <p>11 plausibility specific to Johnson's Baby</p> <p>12 Powder in your report?</p> <p>13 A. If the literature was there,</p> <p>14 there was some -- I'm sorry, I can't</p> <p>15 remember the author now. But there were</p> <p>16 authors and investigators that did use</p> <p>17 Johnson's Baby Powder in their studies,</p> <p>18 and if they used those studies, and I</p> <p>19 used that for -- to provide biological</p> <p>20 plausibility, then yes.</p> <p>21 Q. What studies were done</p> <p>22 specific to Johnson's Baby Powder?</p> <p>23 MS. O'DELL: Object to the</p> <p>24 form.</p>	<p style="text-align: right;">Page 192</p> <p>1 in the question that I was asked to</p> <p>2 comment on, but from cursory knowledge</p> <p>3 there are different cell types.</p> <p>4 Q. What's the difference</p> <p>5 between a low grade and high grade tumor?</p> <p>6 A. The induction of</p> <p>7 invasiveness and proliferation capacity.</p> <p>8 Q. What is thought to be the</p> <p>9 primary origin of high-grade serous</p> <p>10 ovarian cancer?</p> <p>11 MS. O'DELL: Object to the</p> <p>12 form.</p> <p>13 THE WITNESS: Primary</p> <p>14 origin. I'm not sure what that</p> <p>15 means.</p> <p>16 BY MR. HEGARTY:</p> <p>17 Q. Well, what is -- what is</p> <p>18 typically the primary location or origin</p> <p>19 of high-grade serous?</p> <p>20 A. Do you mean in the ovary?</p> <p>21 Q. I don't think I can ask it</p> <p>22 any different way.</p> <p>23 A. Well, I don't quite</p> <p>24 understand your question.</p>
<p style="text-align: right;">Page 191</p> <p>1 THE WITNESS: Of course all</p> <p>2 of the product documents.</p> <p>3 Sorry, I'm having difficulty</p> <p>4 recalling that -- the particular</p> <p>5 name. It's not a memory test.</p> <p>6 I'm sorry.</p> <p>7 BY MR. HEGARTY:</p> <p>8 Q. With regard to ovarian</p> <p>9 cancer, what are the subtypes of the</p> <p>10 disease?</p> <p>11 A. Well, as -- as --</p> <p>12 MS. O'DELL: Object to the</p> <p>13 form.</p> <p>14 THE WITNESS: -- was pointed</p> <p>15 out, I'm not an OB/GYN. I can</p> <p>16 tell you just from cursory</p> <p>17 knowledge that there are serous,</p> <p>18 high grade, low grade serous,</p> <p>19 endometrioid, mucous cell,</p> <p>20 epithelioid.</p> <p>21 BY MR. HEGARTY:</p> <p>22 Q. What are the differences in</p> <p>23 subtypes?</p> <p>24 A. Again, this is not in my --</p>	<p style="text-align: right;">Page 193</p> <p>1 Q. What is the primary origin</p> <p>2 of clear cell carcinoma?</p> <p>3 MS. O'DELL: Object to the</p> <p>4 form.</p> <p>5 THE WITNESS: If you're</p> <p>6 asking me the types, I don't</p> <p>7 recall the type of cell for clear</p> <p>8 cell carcinoma. Again, I'm not an</p> <p>9 OB/GYN, and I'm not a histologist.</p> <p>10 BY MR. HEGARTY:</p> <p>11 Q. For purposes of your report,</p> <p>12 did you analyze biologic plausibility for</p> <p>13 each subtype of ovarian cancer?</p> <p>14 A. No, sir.</p> <p>15 Q. Is it your opinion that the</p> <p>16 etiology of each of the subtypes of</p> <p>17 ovarian cancer is the same?</p> <p>18 A. There are many</p> <p>19 commonalities.</p> <p>20 As I said, from my cursory</p> <p>21 knowledge and my background, early</p> <p>22 background in 1980, of being a --</p> <p>23 pathology when this was not even</p> <p>24 considered or thought about, there is</p>

<p style="text-align: right;">Page 194</p> <p>1 etiologies -- I'm sorry, I had to refresh 2 my memory of your question. 3 There are different 4 etiologies. Many -- and many of the 5 same, and so I think that -- if I may 6 gather my thoughts and refresh your 7 question. 8 So as I said, in terms of my 9 opinion that the etiology in each of the 10 subtypes of ovarian cancer is the same, 11 there are many commonalities in -- 12 etiology being the underlying reason. 13 There are many commonalities for the same 14 cancers, including things like cancer 15 stem cells in ovarian cancer, which are 16 now being identified in the literature as 17 a possibility for recurrence of ovarian 18 cancer. 19 So, yes, there are definite 20 commonalities in terms of the induction 21 of ovarian types of cancer. 22 Q. Well, my question was, is it 23 your opinion that the etiologies of each 24 subtype are the same?</p>	<p style="text-align: right;">Page 196</p> <p>1 Remove your microphones. The time 2 is 12:22 p.m. Off the record. 3 (Lunch break.) 4 THE VIDEOGRAPHER: We are 5 back on the record. The time is 6 1:17 p.m. 7 BY MR. HEGARTY: 8 Q. Doctor, we're back on the 9 record. I want to go back to something 10 we talked about at the beginning, that 11 is, the initial call that you had from 12 Ms. Emmel. 13 You mentioned that you 14 reviewed materials between the time of 15 the call and the time that you agreed to 16 serve as an expert witness. Do you 17 recall saying that? 18 A. I do recall. 19 Q. What materials did you 20 review? 21 A. Just random, whatever I got 22 from the -- that came out using keywords 23 of talc, talcum powder, ovarian cancer. 24 Those were my initial keywords.</p>
<p style="text-align: right;">Page 195</p> <p>1 MS. O'DELL: Objection to 2 form. 3 THE WITNESS: I have -- 4 MS. O'DELL: Asked and 5 answered. 6 THE WITNESS: I have no 7 opinion on that. 8 BY MR. HEGARTY: 9 Q. Is it your opinion -- 10 MS. O'DELL: Excuse me. 11 THE WITNESS: Other than 12 what I -- 13 MS. O'DELL: Sorry. 14 THE WITNESS: I'm sorry. 15 MS. O'DELL: You may finish. 16 I didn't mean to cut you off. 17 THE WITNESS: Other than 18 what I've just given. 19 MS. O'DELL: So, Mark, we've 20 been going about an hour and ten 21 minutes, I think. 22 MR. HEGARTY: Okay. Take a 23 break. 24 THE VIDEOGRAPHER: Stand by.</p>	<p style="text-align: right;">Page 197</p> <p>1 Q. Do you recall, sitting here 2 today, any particular articles, whether 3 by author name or by name of that initial 4 search that you did before agreeing to 5 serve as an expert? 6 A. I looked at Ghio, G-I -- 7 G-H-I-O. Did inhalation of talc and 8 airway cells in in vitro study. 9 I also looked at 10 Dr. De Boers and migration of carbon 11 black material. 12 I also looked at Dr. Venter 13 and Iturralde, who talked about 14 administered radiolabeled microspheres. 15 I read Dr. Weiner's -- 16 Weiner's -- Dr. Weiner's publication. I 17 read Dr. Epstein's letter. 18 Q. Is that something that you 19 found on your own? 20 A. Excuse me. It wasn't 21 Dr. Epstein's letter. I'm sorry. I 22 stand corrected. 23 I read the National 24 Toxicology Report, the NTP 1993.</p>

<p style="text-align: right;">Page 198</p> <p>1 Q. Did you do a more expansive 2 literature search and literature review 3 after agreeing to serve as an expert 4 witness? 5 A. Of course. 6 Q. Did you form any opinions, 7 though, from that initial search that you 8 performed? 9 A. My opinion at that time was 10 that there was certainly -- I had a great 11 deal of interest in the topic, that there 12 was certainly enough information and 13 enough evidence to provide -- that was 14 provided by these publications that -- 15 certainly that particles of the size of 16 talc can be -- can be translocated, 17 migrated, and that -- at least from the 18 lung, and so that there was biological 19 plausibility for movement within the 20 body. 21 And I found it convincing 22 that I could -- that I could get involved 23 in this case and that I believe that 24 there was, at that point with only</p>	<p style="text-align: right;">Page 200</p> <p>1 known about the product is consistent 2 with a cause-and-effect relationship." 3 Do you see that where I'm 4 reading? 5 A. I see where you're reading. 6 Q. Where does that definition 7 of biological plausibility come from? 8 A. It is my professional 9 opinion. 10 Q. Is there still biological 11 plausibility if what is known about a 12 substance and a disease is consistent 13 with no cause-and-effect relationship? 14 MS. O'DELL: Object to the 15 form. 16 THE WITNESS: Biological 17 plausibility, to me, as stated 18 here -- and I will state it a 19 different way, is that there is 20 actually literature and 21 information, reliable, sound 22 science that could -- that 23 provides evidence that there is a 24 mechanism or mechanisms as well as</p>
<p style="text-align: right;">Page 199</p> <p>1 superficial literature searching, that 2 there was indeed room for an opinion. 3 And that opinion being that there 4 certainly was information provided that 5 could lead me to provide biological 6 plausibility in that regard. Otherwise, 7 I would not have taken the case. 8 What I would like to say is 9 that I would have done the same thing if 10 you had called me, sir, to answer the 11 question of what my beliefs are and where 12 the science is. 13 Q. If you look at Page 2 again 14 of your expert report. 15 A. Yes, sir. 16 Q. That's Exhibit 2. Again, 17 under the section mandate -- 18 A. Yes. 19 Q. -- and methodology. 20 A. I see it. 21 Q. You say at the end of the 22 second paragraph that, "Biological 23 plausibility does not mean proof of 24 mechanism, but rather whether what is</p>	<p style="text-align: right;">Page 201</p> <p>1 underlying information that could 2 prove the -- although it's not 3 necessary in Hill's criteria, that 4 could be used to prove a causal 5 relationship. 6 And in this case, that 7 talcum powder, in particular 8 Johnson & Johnson talcum powder, 9 can lead to ovarian cancer. 10 BY MR. HEGARTY: 11 Q. Well, do you agree that the 12 finding of biologic plausibility by 13 itself does not mean causation? 14 A. Biological plausibility is 15 used to supplement or to add on. It is 16 actually one of Hill's criteria. One 17 that he listed in his 1962 paper that is 18 not absolutely necessary but does provide 19 compelling evidence. And I do believe 20 that biological plausibility is extremely 21 important, in my personal opinion, in 22 causal relationship. And Hill agrees to 23 that as well. 24 Q. You agree, though, that the</p>

<p style="text-align: right;">Page 202</p> <p>1 other Hill factors should be applied to 2 determine causality, other than -- in 3 addition to biological plausibility? 4 A. Well, I really can't say. 5 Again, I know -- I know of Hill's work, 6 and I know of his groundbreaking 7 publication. But again, I'm here to talk 8 about plausibility, not causation. 9 Q. At the bottom of Page 2 you 10 say as part of your analysis you 11 reviewed, "Depositions and numerous 12 documents, internal memorandum and 13 published and unpublished studies and 14 testing results that I have found in my 15 own searches of documents, documents 16 provided by attorneys, and documents that 17 I requested." That's carrying over to 18 Page 3. 19 Do you see that? 20 A. Toxicological studies. Are 21 we talking about toxicological studies 22 including in vivo and in vitro? 23 Q. No. I'm looking at the very 24 last sentence of the paragraph at the</p>	<p style="text-align: right;">Page 204</p> <p>1 publication of yours, depositions or 2 expert reports in a litigation? 3 A. No. However, there are 4 papers and regulatory -- regulatory 5 documents that are not considered 6 published, published. If you mean 7 peer-reviewed literature, that's one way 8 of publishing. But another way of 9 publishing is also documents that are in 10 a report. 11 And I have used reports in 12 my own publications, if they -- if they 13 are accessible to me. 14 Q. Have you ever in a published 15 scientific article of yours cited to an 16 expert report from a doctor in a 17 litigation? 18 A. I'm sorry. I have to look 19 down at your question. 20 Not that I recall. But 21 that's not to say that I would not. 22 If it was appropriate for 23 the paper that I was writing, I would 24 certainly use it.</p>
<p style="text-align: right;">Page 203</p> <p>1 bottom of Page 2, carrying over to the 2 top of Page 3? 3 A. In addition, I've reviewed 4 depositions and numerous documents 5 internal memorandum and published and 6 unpublished studies and testing results 7 that I have found in my own searches. 8 Q. Correct. In any scientific 9 analysis that you have done, have you 10 ever included as part of that analysis 11 documents provided by attorneys? 12 A. In my -- when I publish, I 13 look at all relevant information that I 14 have access to. It's about the science. 15 Q. Not my question. My 16 question is in any prior work that you 17 have done where you have published an 18 article, have you included in the review 19 for purposes of publishing that article, 20 documents provided by lawyers? 21 A. No, sir, not to my 22 knowledge. 23 Q. Have you ever included as 24 materials that you have reviewed for any</p>	<p style="text-align: right;">Page 205</p> <p>1 Q. Can you identify any 2 scientific group -- strike that. 3 Before I ask you about 4 causation, now I want to ask you about 5 biological plausibility. Can you cite 6 for me any scientific group, body, or 7 even paper that has concluded that there 8 is biological plausibility between 9 perineal talc use and ovarian cancer? 10 A. Mm-hmm-hmm. If you look at 11 -- I don't know what exhibit it is. But 12 it is the Health Canada report. And -- 13 Canadian U.S. EPA. And if you look at 14 Taher's paper, systemic review and 15 meta-analysis, in both of those -- okay. 16 So the environmental -- Health Canada and 17 Canadian EPA, they put out this -- this 18 document, which is an assessment, a 19 screening assessment document, to look at 20 biological plausibility as well as the 21 other epidemiological literature. 22 And they do speak to the 23 causation and they do speak to biological 24 plausibility of talc and its association</p>

<p style="text-align: right;">Page 206</p> <p>1 or talc and it's causation for ovarian 2 cancer. So they do in that document. 3 The systematic review and 4 meta-analysis 2018 of Taher also speaks 5 of it and reviews the 30 -- I think it's 6 30 -- 30 studies, of which there are 26 7 case-controls and -- studies, and I think 8 four cohort studies. And they do also 9 conclude that, by looking at the 10 meta-analysis, that there are -- that 11 there is causation associated -- that 12 there is causation for talcum powder and 13 ovarian cancer. 14 Q. Actually, Doctor, both 15 documents to which you reference conclude 16 only that perineal use of talcum powder 17 is a possible cause of ovarian cancer, 18 correct? 19 MS. O'DELL: Object to the 20 form. 21 THE WITNESS: They state 22 cause. And if you give me a 23 moment, I can look for it, within 24 the document. So I'm looking at</p>	<p style="text-align: right;">Page 208</p> <p>1 MS. O'DELL: It's Exhibit 9. 2 BY MR. HEGARTY: 3 Q. If you would look -- do you 4 have the Taher review? 5 A. I do. 6 Q. What's that marked as? 7 A. That is Exhibit 10. 8 Q. Exhibit 10? 9 A. Based on your yellow mark, 10 yes. 11 Q. If you look at the abstract 12 under the conclusion section, it 13 concludes that perineal use of talcum 14 powder is a possible cause of human 15 ovarian cancer. 16 Do you see that? 17 A. Excuse me. I dropped my 18 microphone. 19 Okay. Please repeat your 20 question. Your comment. 21 Q. Second page under the 22 conclusion section. The conclusion of 23 the Taher article is, "The perineal use 24 of talc powder is a possible cause of</p>
<p style="text-align: right;">Page 207</p> <p>1 the Health Canada document. 2 Meta -- page -- I'm sorry. 3 Roman Numeral III, "Meta-analysis 4 of the available human studies in 5 the peer-reviewed literature 6 indicate a consistent and 7 statistically significant positive 8 association between perineal 9 exposure to talc and ovarian 10 cancer. Further available data 11 are indicative of causal effect." 12 BY MR. HEGARTY: 13 Q. Okay. What is their 14 ultimate conclusion? 15 A. This is part of their 16 conclusion. 17 Q. Can I look at that document? 18 A. Absolutely. 19 MR. TISI: Is this marked as 20 an exhibit, Mark? 21 MR. HEGARTY: Yes. 22 MR. FINDEIS: Sorry, which 23 number is it marked? So the 24 record is clear.</p>	<p style="text-align: right;">Page 209</p> <p>1 human ovarian cancer," correct? 2 MS. O'DELL: Objection to 3 form. 4 THE WITNESS: I see that 5 conclusion sentence. 6 BY MR. HEGARTY: 7 Q. Nowhere in here do they say 8 that talcum powder causes ovarian cancer, 9 correct? 10 MS. O'DELL: Objection to 11 form. 12 THE WITNESS: If you're 13 looking for a specific sentence, 14 allow me to review. 15 BY MR. HEGARTY: 16 Q. Well, are you going to need 17 to review the entirety of the paper? 18 A. I may. 19 Q. Okay. Well, I can't -- we 20 don't have time for you to review the 21 entirety of the paper so I'll withdraw 22 the question. If you need to review the 23 entirety of the paper. 24 Can you cite here without</p>

Page 210	Page 212
<p>1 reviewing it anywhere where they say 2 talcum powder causes ovarian cancer? 3 A. I cannot -- 4 MS. O'DELL: Excuse me. And 5 you're referring specifically to 6 Exhibit 10? 7 MR. HEGARTY: Correct. 8 MS. O'DELL: The Taher 9 paper? 10 THE WITNESS: I can't say it 11 without looking at the paper. 12 BY MR. HEGARTY: 13 Q. Has the Taher paper been 14 peer reviewed? 15 A. The Taher paper has -- is a 16 document that, yes, has been peer 17 reviewed. To my knowledge. 18 Q. Okay. What publication peer 19 reviewed that document? 20 A. Excuse me? 21 Q. Who peer reviewed that 22 document? 23 A. I have -- I have no 24 knowledge of that.</p>	<p>1 letter, information. And I specifically 2 asked that same question. 3 Q. Now, are you relying on the 4 fact it's been peer reviewed for your 5 opinions in this case? 6 A. I'm relying on the science. 7 Q. Well, are you relying on 8 whether -- on what plaintiffs' counsel 9 told you as far as whether it's been peer 10 reviewed? 11 MS. O'DELL: Object to the 12 form. 13 THE WITNESS: That is what 14 I'm trying to look, whether there 15 is an acknowledgment and whether 16 there is a statement within it 17 which says it's peer reviewed. 18 It -- it's stated that in 19 order for this -- in order for a 20 document such as this, and again 21 it depends on what you mean by 22 peer review, whether it's a 23 community or whether it's the 24 government. The government has</p>
Page 211	Page 213
<p>1 Q. How do you know it's been 2 peer reviewed? 3 A. The -- the plaintiff lawyers 4 have shown me a document, a cover letter, 5 information, I specifically asked that 6 question of them. 7 Q. And are you relying on what 8 they provided to you for purposes of 9 saying it's peer reviewed? 10 A. Please allow me to -- I'm 11 going to take a look into the document 12 again. There may be evidence that's in 13 the document which says it's peer 14 reviewed. 15 Q. Doctor, what are you looking 16 at for purposes of peer review? I asked 17 you -- 18 A. I'm looking to see -- sorry, 19 please finish your question. 20 Q. I asked you how do you know 21 it's been peer reviewed. 22 A. And I stated that the 23 plaintiff lawyer -- the plaintiffs' 24 lawyers have shown me a document, a cover</p>	<p>1 looked at this, and they were 2 submitted by Health Canada, and as 3 of now it's been submitted for 4 peer review, but it was looked at 5 by the Health Canada and by EPA. 6 BY MR. HEGARTY: 7 Q. What document were you shown 8 that shows it's been peer reviewed? 9 A. On the first page, 10 Exhibit 10, materials submitted to Health 11 Canada, materials submitted to journal 12 for peer review. 13 Q. So it's not been peer 14 reviewed? 15 A. To my knowledge, it has been 16 peer reviewed. And again I'm relying on 17 plaintiffs' attorney with that 18 information. 19 Q. Have you ever cited in a 20 scientific article of yours a publication 21 that's not been peer reviewed? 22 A. All the time. 23 Q. So that's something that -- 24 that you have done as part of your</p>

<p style="text-align: right;">Page 214</p> <p>1 methodology?</p> <p>2 MS. O'DELL: Object to the</p> <p>3 form.</p> <p>4 THE WITNESS: It's</p> <p>5 something -- if there is -- based</p> <p>6 on my opinion of the study design,</p> <p>7 the information, the science, if</p> <p>8 it -- if it needs to be stated, if</p> <p>9 the science needs to be out there,</p> <p>10 then I have cited numerous times</p> <p>11 unpublished information.</p> <p>12 BY MR. HEGARTY:</p> <p>13 Q. Do you understand that for</p> <p>14 purposes -- that the -- strike that.</p> <p>15 Do you understand that the</p> <p>16 Health Canada risk assessment is a --</p> <p>17 only a draft assessment at this point in</p> <p>18 time?</p> <p>19 A. It is going to be reviewed,</p> <p>20 yes. I understand that it -- it is a</p> <p>21 draft assessment. I also understand that</p> <p>22 it has gone through scrutiny by both</p> <p>23 Health Canada and Canadian EPA.</p> <p>24 Q. Do you understand that</p>	<p style="text-align: right;">Page 216</p> <p>1 or paper that has concluded that there is</p> <p>2 biologic plausibility between talcum</p> <p>3 powder use and ovarian cancer?</p> <p>4 A. Biological plausibility, in</p> <p>5 my case, and for my review and for my</p> <p>6 report, I'm looking at the inflammation</p> <p>7 as a biological plausibility.</p> <p>8 There is data going back and</p> <p>9 scientific reviews and publications going</p> <p>10 back to the '60s which implicate</p> <p>11 inflammation as a biological mediator for</p> <p>12 cancer.</p> <p>13 Q. Doctor, listen to my</p> <p>14 question. My question is very specific</p> <p>15 to talc and the biologic plausibility</p> <p>16 between talc and ovarian cancer.</p> <p>17 Can you cite for me, besides</p> <p>18 the Canadian documents you cited, any</p> <p>19 scientific group, body or organization</p> <p>20 that has concluded that there is biologic</p> <p>21 plausibility between talcum powder use</p> <p>22 and ovarian cancer?</p> <p>23 A. There is biological</p> <p>24 plausibility and there is evidence that</p>
<p style="text-align: right;">Page 215</p> <p>1 there's a comment period that's going on</p> <p>2 right now?</p> <p>3 A. I understand that, yes.</p> <p>4 Q. And that this is not a final</p> <p>5 statement?</p> <p>6 A. Final statement. In any</p> <p>7 document, any regulatory document that --</p> <p>8 those that are put out by the National</p> <p>9 Academy of Science, whatever document</p> <p>10 you're using, there's always a peer</p> <p>11 review or comment period.</p> <p>12 In my opinion, in my</p> <p>13 professional career, documents do not</p> <p>14 change that drastically based upon the</p> <p>15 comments that come in. Based upon</p> <p>16 National Academy of Science, and the</p> <p>17 National Toxicology Program. There are</p> <p>18 usually not -- there are no -- by the</p> <p>19 time it reaches this point, there are no</p> <p>20 substantive comments that allow for</p> <p>21 extensive changes.</p> <p>22 Q. Other than the Canadian</p> <p>23 documents you just cited, can you cite</p> <p>24 for me any other scientific group, body</p>	<p style="text-align: right;">Page 217</p> <p>1 in Step 1, that talc causes inflammation.</p> <p>2 In Step 2, that inflammation is a</p> <p>3 well-known and well-established factor</p> <p>4 in -- in cancer.</p> <p>5 Q. Doctor, you are not</p> <p>6 answering my question. Do you want to</p> <p>7 read my question? My question is very</p> <p>8 specific.</p> <p>9 Can you cite for me any</p> <p>10 scientific body or group or organization,</p> <p>11 other than what you say the Canadian</p> <p>12 group or groups did, that has concluded</p> <p>13 that there is biologic plausibility</p> <p>14 between talcum powder use and ovarian</p> <p>15 cancer?</p> <p>16 MS. O'DELL: Objection.</p> <p>17 Objection to the question. Asked</p> <p>18 and answered.</p> <p>19 THE WITNESS: I stand by my</p> <p>20 answer. That, again, talc can</p> <p>21 cause inflammation. It's well</p> <p>22 known. And inflammation is an</p> <p>23 underpinning for cancer.</p> <p>24 BY MR. HEGARTY:</p>

<p style="text-align: right;">Page 218</p> <p>1 Q. Okay. Cite for me any 2 scientific group, body or organization 3 who has said that. 4 A. That is throughout 5 literature. If you go back to 1960 and 6 talk about the Vertel and the role of 7 inflammation in cancer, and numerous 8 other publications since that, if you 9 look at -- talc is used to induce 10 pleurodesis because of its inflammatory 11 responsiveness. 12 Q. Doctor, you still are not 13 answering my question. My question is 14 name a scientific body, organization or 15 group who has concluded, as you have 16 done, or you say you do in your paper, 17 that there is biologic plausibility 18 between talc and ovarian cancer. 19 MS. O'DELL: Objection to 20 the form. 21 THE WITNESS: I gave you -- 22 BY MR. HEGARTY: 23 Q. Cite for me the groups. 24 MS. O'DELL: Excuse me. Let</p>	<p style="text-align: right;">Page 220</p> <p>1 biological mechanism that everyone 2 including the National Toxicology, the 3 IARC, the National Academy of Science, 4 EPA, all recognize. 5 Q. Cite for me any group. 6 Again, you are not answering my question. 7 My answer -- 8 A. Okay. 9 Q. -- my question is other than 10 the Canadian groups you've cited, cite 11 for me any group by name who has reached 12 the same opinion as you about biologic 13 plausibility. 14 MS. O'DELL: Objection to 15 form. Other than those she just 16 listed in her last answer? 17 MR. HEGARTY: Well, she 18 didn't list any. I think the 19 record shows that. 20 MS. O'DELL: Yes, she did. 21 MR. HEGARTY: Which ones did 22 she list? 23 MS. O'DELL: NTP. IARC. 24 MR. HEGARTY: Okay. Are you</p>
<p style="text-align: right;">Page 219</p> <p>1 me -- objection to form. Asked 2 and answered. The doctor has 3 answered your question. You may 4 not like the answer, but she's 5 answered it. 6 BY MR. HEGARTY: 7 Q. Cite for me the groups by 8 name. 9 MS. O'DELL: Objection to 10 form. 11 THE WITNESS: Ask the 12 question again? 13 BY MR. HEGARTY: 14 Q. Cite for me any name of any 15 group that has reached the same opinion 16 as you? 17 A. Besides the Health Canada? 18 Q. Correct. 19 A. There are -- I -- you're 20 asking for something that is not -- I'm 21 answering the question by telling you 22 that you have talc which is an 23 inflamagogue, and you have talc and its 24 relationship with cancer. And that is a</p>	<p style="text-align: right;">Page 221</p> <p>1 going on the record to say NTP has 2 concluded that talcum powder use 3 is a biologic 4 plausibility/plausible cause of 5 ovarian cancer? 6 THE WITNESS: We're not -- 7 MS. O'DELL: She was talking 8 about inflammation and cancer, as 9 you well know. 10 MR. HEGARTY: Right, which 11 is why she's not answering my 12 question. 13 MS. O'DELL: No, no. Your 14 question was not in relation to 15 specific talc and biologic 16 plausibility. 17 So the doctor has answered 18 your question. 19 MR. HEGARTY: I think the 20 record will reflect otherwise. 21 BY MR. HEGARTY: 22 Q. Doctor, listen to my 23 question -- 24 MS. O'DELL: No, it will</p>

<p style="text-align: right;">Page 222</p> <p>1 not.</p> <p>2 BY MR. HEGARTY:</p> <p>3 Q. Listen to my question.</p> <p>4 Can you cite for me any</p> <p>5 group besides the Canadian group who has</p> <p>6 concluded that there is biologic</p> <p>7 plausibility, who has made a statement</p> <p>8 that there is biologic plausibility</p> <p>9 between talcum powder use and ovarian</p> <p>10 cancer?</p> <p>11 A. I'm telling -- as I said</p> <p>12 before, you're leaving out the word</p> <p>13 "inflammation."</p> <p>14 Q. Doctor, you -- you need to</p> <p>15 answer the question I ask.</p> <p>16 A. I -- I --</p> <p>17 Q. Your counsel can come back</p> <p>18 and ask you that question. I under -- I</p> <p>19 want to know the name of any organization</p> <p>20 by name who has concluded that there is</p> <p>21 biologic plausibility between perineal</p> <p>22 use of talc and ovarian cancer.</p> <p>23 A. Anyone --</p> <p>24 MS. O'DELL: Other than the</p>	<p style="text-align: right;">Page 224</p> <p>1 I've shown, whether it's in air pollution</p> <p>2 or whether it's in tobacco products or</p> <p>3 nicotine products or World Trade Center</p> <p>4 dust or metal inhalation or nanoparticle</p> <p>5 inhalation. They all give biological</p> <p>6 plausibility statements for the</p> <p>7 observations that have been found in my</p> <p>8 laboratory.</p> <p>9 Q. Where have you ever</p> <p>10 published step-by-step methodology for</p> <p>11 how you go about determining whether</p> <p>12 there is biological plausibility between</p> <p>13 a substance and a disease?</p> <p>14 A. I use my professional</p> <p>15 judgment.</p> <p>16 Q. Have you ever published that</p> <p>17 professional judgment?</p> <p>18 MS. O'DELL: Objection to</p> <p>19 form.</p> <p>20 THE WITNESS: I don't think</p> <p>21 that would be publishable</p> <p>22 material.</p> <p>23 BY MR. HEGARTY:</p> <p>24 Q. In the end, Doctor, your</p>
<p style="text-align: right;">Page 223</p> <p>1 ones she -- she's listed.</p> <p>2 THE WITNESS: Anyone that</p> <p>3 you say -- any -- I'll do it</p> <p>4 again. National Toxicology</p> <p>5 Program. IARC. Institute of</p> <p>6 Medicine.</p> <p>7 They may not say the</p> <p>8 sentence you are -- you are</p> <p>9 implying or you're stating. But</p> <p>10 they all show that talc has --</p> <p>11 produces inflammation.</p> <p>12 I don't think that the -- I</p> <p>13 think that's a very common</p> <p>14 knowledge that talc or talcum</p> <p>15 powder products does produce</p> <p>16 inflammation.</p> <p>17 BY MR. HEGARTY:</p> <p>18 Q. Doctor, where have you ever</p> <p>19 published a methodology for determining</p> <p>20 whether there is biologic plausibility</p> <p>21 between an exposure and a disease?</p> <p>22 A. Almost every paper that I</p> <p>23 have in my CV talks about the biological</p> <p>24 plausibility for the observations that</p>	<p style="text-align: right;">Page 225</p> <p>1 report is your subjective take on the</p> <p>2 studies, correct?</p> <p>3 MS. O'DELL: Objection to</p> <p>4 form.</p> <p>5 BY MR. HEGARTY:</p> <p>6 Q. I mean, you don't speak for</p> <p>7 any scientific group, do you?</p> <p>8 A. I'm an expert toxicologist,</p> <p>9 recognized clearly by the Society of</p> <p>10 Toxicology as an expert in my field.</p> <p>11 And -- I'm sorry. I --</p> <p>12 Q. Well, is your report</p> <p>13 speaking for the society --</p> <p>14 MS. O'DELL: Excuse me.</p> <p>15 BY MR. HEGARTY:</p> <p>16 Q. Is your report speaking for</p> <p>17 the Society of Toxicology?</p> <p>18 MS. O'DELL: She wasn't</p> <p>19 finished.</p> <p>20 THE WITNESS: I wasn't. I</p> <p>21 was --</p> <p>22 MS. O'DELL: She wasn't</p> <p>23 finished. Please let the witness</p> <p>24 finish.</p>

<p style="text-align: right;">Page 226</p> <p>1 MR. HEGARTY: I'll withdraw</p> <p>2 the question.</p> <p>3 BY MR. HEGARTY:</p> <p>4 Q. Doctor, do you speak for the</p> <p>5 Society of Toxicology for purposes of</p> <p>6 your opinions in your report?</p> <p>7 A. No.</p> <p>8 Q. Do you speak for any</p> <p>9 society, any toxicology society --</p> <p>10 society for purposes of your opinions?</p> <p>11 A. You didn't let me finish my</p> <p>12 answer.</p> <p>13 I do not speak for the</p> <p>14 society of toxicology. But I am a</p> <p>15 recognized toxicology expert, recognized</p> <p>16 by the Society of Toxicology as an</p> <p>17 expert. And I have written this report</p> <p>18 based upon literature, scientific</p> <p>19 evidence, and my professional judgment.</p> <p>20 Q. What society has recognized</p> <p>21 you as an expert in talc and ovarian</p> <p>22 cancer?</p> <p>23 A. I'm recognized as expert in</p> <p>24 toxicology.</p>	<p style="text-align: right;">Page 228</p> <p>1 form.</p> <p>2 You can answer.</p> <p>3 THE WITNESS: This is my</p> <p>4 opinion based upon my systematic</p> <p>5 review of all the scientific</p> <p>6 literature. And they -- by the</p> <p>7 nature of hiring me, they have</p> <p>8 approved of my -- my opinions.</p> <p>9 Maybe not specifically in this</p> <p>10 case, but they would not have</p> <p>11 hired me or kept me for 35 years</p> <p>12 if they did not agree that I was a</p> <p>13 well-known established</p> <p>14 toxicologist whose opinions are</p> <p>15 based in my professional judgment.</p> <p>16 BY MR. HEGARTY:</p> <p>17 Q. Did you tell the university,</p> <p>18 New York University, of your opinions in</p> <p>19 this case?</p> <p>20 A. I did not.</p> <p>21 Q. Have you told them that</p> <p>22 you're an expert witness for plaintiffs</p> <p>23 in this litigation?</p> <p>24 A. I have, yes.</p>
<p style="text-align: right;">Page 227</p> <p>1 Q. What society has --</p> <p>2 A. Society of Toxicology.</p> <p>3 Q. Has the Society of</p> <p>4 Toxicology recognized you as an expert in</p> <p>5 talc and ovarian cancer?</p> <p>6 MS. O'DELL: Objection to</p> <p>7 form.</p> <p>8 THE WITNESS: I was</p> <p>9 recognized as an expert in tox and</p> <p>10 ovarian cancer and talc by the</p> <p>11 very basis that I'm sitting here.</p> <p>12 BY MR. HEGARTY:</p> <p>13 Q. You don't speak for your</p> <p>14 university, do you?</p> <p>15 A. No one -- no one speaks</p> <p>16 directly for the university. But what we</p> <p>17 say, we understand our paychecks come</p> <p>18 from the university, and we follow within</p> <p>19 the university and the medical school</p> <p>20 guidelines.</p> <p>21 Q. Are your opinions in this</p> <p>22 case the opinions of New York University?</p> <p>23 A. This is my --</p> <p>24 MS. O'DELL: Objection to</p>	<p style="text-align: right;">Page 229</p> <p>1 Q. Have you reported, in your</p> <p>2 financial disclosure, the money that</p> <p>3 you've made in this litigation?</p> <p>4 A. Up until -- we are asked</p> <p>5 that question -- we have to fill out</p> <p>6 reports on transparency and conflicts of</p> <p>7 interest. And I think the last time I</p> <p>8 did it was in November of 2018. And I</p> <p>9 reported up to that time, yes. We are</p> <p>10 required to do that and, yes, I am</p> <p>11 completely transparent.</p> <p>12 So any money that I've made</p> <p>13 since November, or since the filing of</p> <p>14 the confidentiality agreement has not</p> <p>15 been reported but will be coming in March</p> <p>16 or April.</p> <p>17 Q. You don't speak for any</p> <p>18 journal for the purpose of your report,</p> <p>19 do you?</p> <p>20 A. For purposes of this report</p> <p>21 I do not speak for journals. But I do</p> <p>22 speak for journals because I'm an editor,</p> <p>23 I'm an associate editor and on the</p> <p>24 editorial boards for numerous</p>

<p style="text-align: right;">Page 230</p> <p>1 environmental health and toxicology 2 journals. 3 Q. At the top of Page 3 of your 4 report, you say in the first full 5 paragraph that you considered the studies 6 that did not find an increased risk of 7 ovarian cancer with talc use. 8 Do you see that? 9 MS. O'DELL: What page are 10 you on? I'm sorry. 11 BY MR. HEGARTY: 12 Q. Page 3. 13 A. I'm sorry. I know we're on 14 Page 3. 15 Q. The first full paragraph. 16 A. My opinions below? 17 Q. The first full paragraph. 18 A. My opinions below. "My 19 opinions below" -- 20 Q. At the very -- at the very 21 end, you say you considered those studies 22 that did not find an increased risk. 23 Do you see that? 24 A. I'm reading it.</p>	<p style="text-align: right;">Page 232</p> <p>1 several, there are case-control 2 studies as well as cohort studies 3 which showed negative 4 associations. 5 BY MR. HEGARTY: 6 Q. You did not cite any of 7 those in your report, though, did you? 8 A. No. What I said -- I'm 9 sorry. Let me try and make it clear. 10 Yes, those meta-analyses 11 were included in the report or -- I need 12 to find the names. Systematic review 13 that I cited was 14 P-E-N-N-I-N-K-I-L-A-M-P-I 2018. And that 15 was a meta-analysis which reviewed the 16 epidemiological case-control and cohort 17 studies which showed that there were 18 studies that had negative associations. 19 Q. Is that the only reference 20 that you included in your report, to 21 studies that did not find an increased 22 risk of ovarian cancer with talc use? 23 MS. O'DELL: Object to the 24 form.</p>
<p style="text-align: right;">Page 231</p> <p>1 Yes, okay. You were reading 2 in the middle of the sentence. "To my 3 knowledge, I considered and evaluated the 4 majority of all available relevant 5 studies in the process of evaluating the 6 literature, including those that reported 7 an elevated risk of ovarian cancer with 8 exposure to talc and those where other 9 chemicals were reported within talc-based 10 body powders, including those that did 11 not find an increased risk." Yes. 12 Q. You did not cite a single 13 paper in your report that did not find an 14 increased risk of ovarian cancer with 15 talc use, did you? 16 MS. O'DELL: Objection to 17 form. 18 THE WITNESS: There were -- 19 in reading over the meta-analysis 20 of -- I'm sorry, I'm probably 21 going to get his name wrong -- 22 Penninkilampi. 23 In reading over the 24 meta-analysis of several -- from</p>	<p style="text-align: right;">Page 233</p> <p>1 THE WITNESS: No. No. 2 MS. O'DELL: Excuse me. 3 Object to the form. 4 THE WITNESS: No. Under the 5 animal models on Page 13, there 6 were -- with rats that were 7 exposed by the peritoneum -- 8 perineum, sorry, to either talc or 9 no treatment. And while they did 10 find inflammatory response -- 11 again, going back to my biological 12 plausibility -- they did not find 13 neoplasms. 14 BY MR. HEGARTY: 15 Q. So that would be an example 16 of a study that did not show an increased 17 risk of ovarian cancer with talc use, 18 correct? 19 A. That is -- 20 MS. O'DELL: Object to the 21 form. 22 Go ahead. 23 BY MR. HEGARTY: 24 Q. Is that correct?</p>

<p style="text-align: right;">Page 234</p> <p>1 A. Sorry. Repeat the question. 2 Repeat the question, please. 3 Q. Sure. So that is an example 4 of a study that, in your opinion, does 5 not show an increased risk of ovarian 6 cancer with talc use? 7 MS. O'DELL: Objection to 8 form. Go ahead. Sorry. 9 THE WITNESS: Sorry. 10 This is a study which shows 11 biological plausibility by showing 12 that there is a foreign body 13 reaction and inflammatory 14 response. However, it does not 15 show that there was any change in 16 neoplasm -- or any induction of 17 neoplasms or cancer. 18 BY MR. HEGARTY: 19 Q. Did you read any cell study 20 that showed that talc is not cytotoxic? 21 A. Can you please explain what 22 you mean by cytotoxic? I want to answer 23 the question as you understand it. 24 Q. What is your definition of</p>	<p style="text-align: right;">Page 236</p> <p>1 showing that talc was not toxic to cells? 2 A. I read comparison studies. 3 Let me please find that, the exact names. 4 Q. Let me withdraw the 5 question. Doctor, in your opinion is 6 talc mutagenic? 7 A. How do you define 8 "mutagenic"? 9 Q. Doctor, what's your -- 10 mutagenic is mutation to genes. Does 11 talc mutate genes? 12 A. Talc leads to changes in 13 gene expression which can be inferred as 14 a mutation. However, when you talk about 15 mutation, you have many different 16 mechanisms of mutation. Mutation can 17 occur as a result of a genotoxic or 18 direct impact on DNA, or it can occur as 19 a result of changes in the epigenome, 20 which leads to changes in expression of 21 the gene. 22 Q. Does talc directly mutate 23 genes? 24 A. Talc has been shown to</p>
<p style="text-align: right;">Page 235</p> <p>1 cytotoxicity? 2 A. I'd like to answer the 3 question that you're asking me. 4 Q. I'm asking you your 5 definition. The way a deposition works 6 is I ask you questions. You don't ask me 7 questions. 8 MS. O'DELL: Don't be -- be 9 courteous to the witness, please. 10 MR. HEGARTY: I am. 11 THE WITNESS: I appreciate 12 that. I just want to, as a 13 toxicologist, the word 14 "cytotoxicity" carries many 15 meanings. 16 BY MR. HEGARTY: 17 Q. What is your definition -- 18 basic definition of cytotoxicity? 19 A. There are many meanings. 20 Cytotoxicity taken literally meaning 21 toxicity to a cell. Cyto, cell; 22 toxicity, toxic. However, toxicity can 23 be measured by numerous endpoints. 24 Q. Did you read any studies</p>	<p style="text-align: right;">Page 237</p> <p>1 cause -- to cause changes in particular 2 enzymes in the gene expression. So a 3 mutation -- yes, it has been -- it has 4 been shown for mutation. But I just 5 need -- I need the attorneys to 6 understand that there are many ways to 7 mutate a cell, not only can you do it by 8 chemical agent, but you can also -- it 9 occurs with aging. 10 So you do not need -- I'm 11 sorry. You do not need genotoxicity to 12 produce mutagenesis. 13 Now, if you look at many 14 different assays such as the Ames assay 15 which uses bacteria to assess 16 mutagenicity, you are not going to see 17 that as a possibility for talc because 18 the bacteria cannot engulf the particle 19 and the particle needs to be ingested in 20 order to show mutagenesis. 21 Q. Doctor, on Page 4 above your 22 section "fibrous talc" -- 23 A. I see it. 24 Q. -- you refer to particle</p>

<p style="text-align: right;">Page 238</p> <p>1 size for talc.</p> <p>2 A. That's correct.</p> <p>3 Q. Is knowing particle size</p> <p>4 part of your methodology for your</p> <p>5 opinions in your report?</p> <p>6 A. I'm sorry. I don't</p> <p>7 understand what you mean by was it part</p> <p>8 of my methodology.</p> <p>9 Q. Well, what is the threshold</p> <p>10 size of a talc particle to establish</p> <p>11 biologic plausibility?</p> <p>12 MS. O'DELL: Object to form.</p> <p>13 THE WITNESS: I don't think</p> <p>14 you can answer that question.</p> <p>15 In -- let me say this.</p> <p>16 In doing my methodology and</p> <p>17 accumulating literature, I -- as I</p> <p>18 said, I binned or siloed</p> <p>19 individual things.</p> <p>20 And one of the silos and one</p> <p>21 of the categories that I -- that I</p> <p>22 wanted to read was size. Size</p> <p>23 makes a very big difference in</p> <p>24 particles, and for example, if the</p>	<p style="text-align: right;">Page 240</p> <p>1 THE WITNESS: Establishing</p> <p>2 my biological plausibility was --</p> <p>3 was travel -- is traveling through</p> <p>4 migration and the ability for a --</p> <p>5 for the powder to migrate or the</p> <p>6 constituents to migrate. And --</p> <p>7 and also the ability to be</p> <p>8 inflammatory.</p> <p>9 BY MR. HEGARTY:</p> <p>10 Q. Well, what size -- what size</p> <p>11 of particle -- what size must the</p> <p>12 particle be to cause inflammation that</p> <p>13 leads to ovarian cancer?</p> <p>14 A. Particles of any --</p> <p>15 MS. O'DELL: Objection to</p> <p>16 form. You may go.</p> <p>17 THE WITNESS: Particles of</p> <p>18 any size can cause inflammation.</p> <p>19 BY MR. HEGARTY:</p> <p>20 Q. What about talc particles,</p> <p>21 what size of talc particle must there be</p> <p>22 to cause inflammation?</p> <p>23 A. Talc particles of any size</p> <p>24 can cause inflammation.</p>
<p style="text-align: right;">Page 239</p> <p>1 particle is greater than</p> <p>2 10 microns it's going to be what</p> <p>3 we call inhalable as opposed to</p> <p>4 respirable. So where a particle</p> <p>5 can go in terms of, and now I'm</p> <p>6 using the lung as an example,</p> <p>7 where the particle can go will</p> <p>8 depend upon its size and how long</p> <p>9 it will remain in a tissue.</p> <p>10 So in my bins, in my silos</p> <p>11 were -- certainly size was a</p> <p>12 parameter.</p> <p>13 BY MR. HEGARTY:</p> <p>14 Q. And what is the threshold</p> <p>15 size of a talc particle to establish</p> <p>16 biologic plausibility between talc and</p> <p>17 ovarian cancer?</p> <p>18 MS. O'DELL: Objection to</p> <p>19 the form.</p> <p>20 BY MR. HEGARTY:</p> <p>21 Q. What size must the particle</p> <p>22 be?</p> <p>23 MS. O'DELL: Objection to</p> <p>24 form.</p>	<p style="text-align: right;">Page 241</p> <p>1 Q. And is there --</p> <p>2 A. However, there are</p> <p>3 differences, from reading the literature,</p> <p>4 that indicates that the smaller the</p> <p>5 particle the greater the inflammation.</p> <p>6 And that's universally</p> <p>7 known.</p> <p>8 Q. Was part of your analysis,</p> <p>9 did you -- did that involve investigating</p> <p>10 biologic plausibility as it relates to</p> <p>11 particle size?</p> <p>12 A. That was -- that was part of</p> <p>13 my reading and part of my -- my thought</p> <p>14 process, my gathering of information,</p> <p>15 yes.</p> <p>16 Q. And is there a certain size</p> <p>17 of particle necessary to establish</p> <p>18 biologic plausibility under your opinion?</p> <p>19 MS. O'DELL: Objection.</p> <p>20 Asked and answered.</p> <p>21 THE WITNESS: Well, I do</p> <p>22 think I answered that question.</p> <p>23 But again there's really --</p> <p>24 apart -- it is not just particle</p>

<p style="text-align: right;">Page 242</p> <p>1 size which is important in 2 producing an inflammation. It is 3 many parameters. And so there was 4 no one size or one cutoff that 5 induces inflammation or does not. 6 It's chemical composition, it's 7 shape of the particle, it's 8 bioavailability of the particle. 9 BY MR. HEGARTY: 10 Q. Can you cite for me the -- 11 the particle size for Johnson's Baby 12 Powder over the last 120 years? 13 MS. O'DELL: Objection to 14 form. 15 THE WITNESS: I'm not sure I 16 can cite it over the last 17 120 years. But I can tell you 18 from the information in the 19 documents that I -- that I 20 reviewed, that particle size goes 21 from above 50 microns, 22 micrometers, microns, down to 23 0.3 micron with an average size of 24 10.5 to 11.5 depending on the</p>	<p style="text-align: right;">Page 244</p> <p>1 Q. Well, fibrous talc is only 2 talc that grows in an -- in an 3 asbestiform habit, correct? 4 A. Fibrous talc refers to the 5 shape and the longitudinal direction of 6 the fibers. That's what fibrous talc is, 7 and asbestiform refers to the same 8 longitudinal pattern of the particular 9 fibrils and -- to form a bundle or to 10 form a fiber. 11 Q. So you don't agree that 12 fibrous talc is only talc that grows in 13 an asbestiform habit? 14 MS. O'DELL: Objection to 15 form. 16 THE WITNESS: Fibrous talc 17 by its very nature is saying that 18 it grows in an asbestiform-like 19 phenotype or asbestiform-like 20 morphology. That's the nature of 21 asbestiform. 22 Asbestiform is a form. 23 BY MR. HEGARTY: 24 Q. You state in the middle</p>
<p style="text-align: right;">Page 243</p> <p>1 document that you read. So an 2 average or median size. 3 BY MR. HEGARTY: 4 Q. So did you -- did you do 5 analysis for biologic plausibility 6 purposes of every size of talc particle? 7 MS. O'DELL: Objection. 8 Asked and answered. 9 THE WITNESS: Did I do 10 analysis -- I -- no, as I said, I 11 gave you the size of the -- of the 12 talcum that was reviewed, that I 13 reviewed within the documents. 14 BY MR. HEGARTY: 15 Q. You, on -- on page -- strike 16 that. 17 Under the section Fibrous 18 Talc, you say that -- is it your 19 testimony that -- strike that. 20 Is it your opinion that 21 asbestiform talc is also called fibrous 22 talc? 23 A. Talc and asbestos are -- are 24 different minerals.</p>	<p style="text-align: right;">Page 245</p> <p>1 paragraph, in that section, that talc in 2 its fibrous form has been classified by 3 IARC as Group I, a known carcinogen. 4 That's not correct, is it? 5 MS. O'DELL: Objection to 6 form. 7 THE WITNESS: I'm sorry, 8 could you say again? 9 BY MR. HEGARTY: 10 Q. Well, you agree that only 11 talc containing asbestiform fibers has 12 been classified as Group I by IARC, 13 correct? 14 A. Are you referring to in 2010 15 IARC expanded or -- I'm sorry, in its 16 fibrous form, talc has been classified as 17 a Group I known carcinogen? 18 Q. Correct. 19 A. Asbestiform fibers have been 20 listed by IARC as a carcinogen. 21 Q. A talc containing 22 asbestiform fibers is the only form of 23 talc that's been designated as a class -- 24 as a Category I carcinogen by IARC,</p>

<p style="text-align: right;">Page 246</p> <p>1 correct?</p> <p>2 A. It's not the only one that's</p> <p>3 been associated with it, but for the</p> <p>4 purpose of my report that I put down,</p> <p>5 it's the asbestiform that has been</p> <p>6 classified by the IARC.</p> <p>7 Q. Well, it's talc containing</p> <p>8 asbestiform fibers, correct?</p> <p>9 MS. O'DELL: Objection to</p> <p>10 form.</p> <p>11 THE WITNESS: It's -- it's</p> <p>12 fibrous talc.</p> <p>13 BY MR. HEGARTY:</p> <p>14 Q. Is that -- that's your --</p> <p>15 your -- it's your opinion that IARC's</p> <p>16 designation in 2012 is of asbestiform</p> <p>17 talc?</p> <p>18 A. Their designations is</p> <p>19 form -- is talc fibers, which are</p> <p>20 asbestiform in nature.</p> <p>21 Q. Do you cite to any published</p> <p>22 data in the medical literature that</p> <p>23 asbestiform talc has been found in</p> <p>24 Johnson's Baby Powder?</p>	<p style="text-align: right;">Page 248</p> <p>1 Can you cite for me any published medical</p> <p>2 literature finding asbestiform talc in</p> <p>3 Johnson's Baby Powder?</p> <p>4 A. Page 6 of my report speaks</p> <p>5 of the Crowley report, and that the fiber</p> <p>6 content ranged from 8 percent to</p> <p>7 30 percent. And that Pooley and Rohl</p> <p>8 analyzed 27 talc powders and detected</p> <p>9 tremolite fibers in three samples.</p> <p>10 Q. Is it your testimony that</p> <p>11 Crowley -- Crowley's article refers to</p> <p>12 Johnson's Baby Powder?</p> <p>13 A. I would have to see the</p> <p>14 article.</p> <p>15 Q. How about Pooley and Rohl,</p> <p>16 do they refer to Johnson's Baby Powder?</p> <p>17 A. I would have to see the</p> <p>18 article.</p> <p>19 Q. In the end, for purposes of</p> <p>20 your opinion as to asbestos and talc,</p> <p>21 you're relying on the report of Longo and</p> <p>22 Rigler, correct?</p> <p>23 MS. O'DELL: Objection to</p> <p>24 form.</p>
<p style="text-align: right;">Page 247</p> <p>1 A. I'm sorry.</p> <p>2 You cite -- do you cite to</p> <p>3 any published data in the medical</p> <p>4 literature that asbestiform talc...</p> <p>5 The documents, the published</p> <p>6 documents within Johnson & Johnson and</p> <p>7 the Longo report, Longo's 2017, as well</p> <p>8 as 2018 supplement from December, shows</p> <p>9 asbestiform fibers.</p> <p>10 Q. My question though is can</p> <p>11 you cite any data published in the</p> <p>12 medical literature that has found</p> <p>13 asbestiform talc in Johnson's Baby</p> <p>14 Powder?</p> <p>15 A. I thought I just did in</p> <p>16 terms of the Longo report.</p> <p>17 Q. Is the Longo report</p> <p>18 published in the medical literature?</p> <p>19 A. It's -- I'm not sure whether</p> <p>20 it's accessible in the medical -- medical</p> <p>21 literature at this point. But I'm sure</p> <p>22 it could be gathered.</p> <p>23 Q. My -- my question is solely</p> <p>24 as to the published medical literature.</p>	<p style="text-align: right;">Page 249</p> <p>1 THE WITNESS: No, I rely on</p> <p>2 the scientific literature, not on</p> <p>3 any one paper. I used weight of</p> <p>4 evidence to come to my opinion.</p> <p>5 BY MR. HEGARTY:</p> <p>6 Q. Did you include in your</p> <p>7 weighing of evidence the expert reports</p> <p>8 of Longo and Rigler?</p> <p>9 A. I read the Longo supplement</p> <p>10 2018 after I wrote the report.</p> <p>11 Q. For purposes -- for purposes</p> <p>12 of the opinions again in this case, do</p> <p>13 you rely in any way on the Longo and</p> <p>14 Rigler reports?</p> <p>15 MS. O'DELL: Objection to</p> <p>16 form.</p> <p>17 THE WITNESS: I'm not sure I</p> <p>18 understand your question. As I</p> <p>19 said, I wrote the report on</p> <p>20 November 16th. I read the Longo</p> <p>21 supplement report in -- about two</p> <p>22 weeks ago.</p> <p>23 BY MR. HEGARTY:</p> <p>24 Q. But you cite in your report</p>

<p style="text-align: right;">Page 250</p> <p>1 the -- the MDL report of Longo and 2 Rigler, correct? 3 A. What page is that please? 4 Q. At the end of Exhibit B. 5 A. I -- okay. 6 Excuse me. I referred to 7 Longo on page -- there is no page. 8 Sorry. 9 The cosmetic talc in the 10 Lancet and cosmetic talc in -- and 11 ovarian cancer in the Lancet. Those are 12 very early papers which I -- which I 13 reviewed. Those papers were considered. 14 The latest papers from Longo were not 15 considered in my report. 16 Q. Are you talking about the 17 latest -- 18 A. 2017, 2018. They were not 19 read until after the report was 20 finalized. 21 Q. Do you know Longo and 22 Rigler? 23 A. Not at all. 24 THE VIDEOGRAPHER: Doctor,</p>	<p style="text-align: right;">Page 252</p> <p>1 use, the polarized light 2 microscopy and the TEM all seem to 3 be the way he describes it. His 4 methodologies were spot on in 5 terms of what other people do. 6 BY MR. HEGARTY: 7 Q. Are you an expert in XRD? 8 A. As I stated, I worked with 9 people who used the instrumentation. An 10 expert, again, I'm not sure what you mean 11 by expert. Have I done XRD on my own, 12 no. But in our department we have 13 numerous people who -- who use that 14 instrumentation. 15 Q. Are you an expert in TEM? 16 A. I have done TEM for my Ph.D. 17 thesis. 18 Q. Have you do TEM -- have you 19 ever done TEM to detect asbestos? 20 A. I have not done TEM to 21 detect asbestos. But I looked at his 22 methodologies, his study design, and the 23 instruments that he used. And they are 24 state of the art.</p>
<p style="text-align: right;">Page 251</p> <p>1 can you raise your microphone up? 2 THE WITNESS: Oh, sure. 3 BY MR. HEGARTY: 4 Q. Did you do anything to 5 assess their expertise in this area? 6 A. I -- I -- 7 MS. O'DELL: Are you 8 referring to Dr. Longo and 9 Dr. Rigler? 10 MR. HEGARTY: Yes. 11 THE WITNESS: I read the -- 12 the bio sketch, a brief, very 13 brief bio sketch of Ray Longo. 14 And I looked up his credentials in 15 terms of how long he's been in 16 the -- in this company, how he 17 started this company or at least 18 was president of this company for 19 a short period of time. 20 From what I know of my own 21 work in the laboratory and working 22 with other chemists and technical 23 instrumentation people in the 24 laboratory, I -- the XRD that they</p>	<p style="text-align: right;">Page 253</p> <p>1 Q. Have you ever performed the 2 test that he describes in his articles or 3 reports? 4 A. I have used polarized light 5 microscopy. 6 Q. That's not my question. My 7 question is have you performed the same 8 tests in your lab or in any -- in your 9 experience that he has performed and 10 reported on in his reports? 11 A. Personally, no. 12 Q. Starting on Page 5, you talk 13 about asbestos. 14 A. Page 5 of what? 15 Q. Of your report. 16 A. Thank you. 17 Q. Is it your opinion that any 18 amount of exposure to asbestos, even to a 19 single fiber, can cause disease? 20 A. From the scientific 21 literature it is -- it appears -- it 22 appears pretty conclusive that there is 23 no threshold for the amount of 24 asbestiform asbestos that is needed to at</p>

<p style="text-align: right;">Page 254</p> <p>1 least start a disease process.</p> <p>2 Q. Before being contacted by</p> <p>3 counsel for plaintiffs in this case, had</p> <p>4 you read any literature concerning</p> <p>5 asbestos and ovarian cancer?</p> <p>6 A. I have not read literature</p> <p>7 prior to that on asbestos and ovarian</p> <p>8 cancer. However, I am familiar with, as</p> <p>9 I said, other particles, other dusts,</p> <p>10 other fibers that I have worked with in</p> <p>11 the laboratory.</p> <p>12 Q. Had you even heard of a link</p> <p>13 between asbestos and ovarian cancer</p> <p>14 before being contacted by plaintiffs'</p> <p>15 counsel?</p> <p>16 A. Yes.</p> <p>17 Q. Where did you hear that</p> <p>18 from?</p> <p>19 A. Discussed it with my</p> <p>20 colleagues. As I said, I've listened to</p> <p>21 the media on discussing it. And my</p> <p>22 colleagues are a very good source,</p> <p>23 although they do not do this work in</p> <p>24 their laboratory, we all try to keep up</p>	<p style="text-align: right;">Page 256</p> <p>1 THE WITNESS: I don't think</p> <p>2 that's -- I don't think that's --</p> <p>3 I don't personally think that's</p> <p>4 the question.</p> <p>5 The question is, asbestos is</p> <p>6 well classified, well known as a</p> <p>7 Class 1 carcinogen by IARC. And</p> <p>8 one fiber has the potential to</p> <p>9 initiate the biological processes</p> <p>10 or provides biological</p> <p>11 plausibility that there, in fact,</p> <p>12 by producing inflammation and</p> <p>13 producing reactive oxygen</p> <p>14 intermediates, one fiber can start</p> <p>15 the process for ovarian cancer.</p> <p>16 And again, let me just</p> <p>17 repeat that my mission, my</p> <p>18 question that was asked, was to</p> <p>19 provide biological plausibility</p> <p>20 for talc, not to define causation</p> <p>21 as an epidemiologist.</p> <p>22 BY MR. HEGARTY:</p> <p>23 Q. So it's your opinion that a</p> <p>24 single fiber of asbestos in talc can</p>
<p style="text-align: right;">Page 255</p> <p>1 with the latest emerging scientific</p> <p>2 debates.</p> <p>3 Q. What is the minimum number</p> <p>4 of asbestos fibers necessary to cause</p> <p>5 ovarian cancer?</p> <p>6 A. Can -- do you mean -- I said</p> <p>7 that there is really no threshold. And</p> <p>8 it can be one fiber. It depends on the</p> <p>9 individual and the susceptibilities and</p> <p>10 the vulnerabilities of that particular</p> <p>11 individual.</p> <p>12 Q. So it's your opinion that</p> <p>13 one fiber of asbestos can cause ovarian</p> <p>14 cancer?</p> <p>15 A. Under certain conditions,</p> <p>16 yes, it is my opinion.</p> <p>17 Q. Can you cite for me any</p> <p>18 authority for that opinion specific to</p> <p>19 one fiber?</p> <p>20 MS. O'DELL: Object to form.</p> <p>21 BY MR. HEGARTY:</p> <p>22 Q. And ovarian cancer.</p> <p>23 MS. O'DELL: Object to the</p> <p>24 form.</p>	<p style="text-align: right;">Page 257</p> <p>1 establish biological plausibility between</p> <p>2 talc and ovarian cancer?</p> <p>3 A. My --</p> <p>4 MS. O'DELL: Object to the</p> <p>5 form.</p> <p>6 THE WITNESS: My opinion is</p> <p>7 that a single fiber can induce</p> <p>8 inflammation and reactive oxygen</p> <p>9 species and can change the cell</p> <p>10 into a pro-oxidant cell that</p> <p>11 starts the process for ovarian</p> <p>12 cancer.</p> <p>13 BY MR. HEGARTY:</p> <p>14 Q. Do you agree that there are</p> <p>15 background rates of asbestos in certain</p> <p>16 areas?</p> <p>17 A. Do you mean in the air?</p> <p>18 Q. In the air?</p> <p>19 A. In the air, it depends on</p> <p>20 that area. If that's an area where</p> <p>21 there's mining or there's a house being</p> <p>22 redone from the 1970s or 19 -- early '80s</p> <p>23 that might have used asbestos, then there</p> <p>24 will be asbestos in the air. But not</p>

<p style="text-align: right;">Page 258</p> <p>1 sitting in this room, unless there is 2 asbestos in the walls, which I doubt 3 because it was only built about ten years 4 ago. 5 Q. Do the background rates of 6 asbestos in certain areas cause ovarian 7 cancer? 8 A. Asbestos has been shown to 9 cause ovarian cancer by inhalation, yes. 10 Q. Is it your opinion that 11 background rates of asbestos in the air 12 can cause ovarian cancer? 13 MS. O'DELL: Object to the 14 form. 15 THE WITNESS: I don't -- 16 again, background rates, it has 17 been shown that workers that are 18 in places where asbestos is made 19 have a higher incidence of lung 20 cancer as shown by Dr. Selikoff 21 many, many years ago. 22 BY MR. HEGARTY: 23 Q. Doctor, you know what a 24 background rate of -- background level of</p>	<p style="text-align: right;">Page 260</p> <p>1 A. It depends. After the World 2 Trade Center, there was. 3 Q. Are those background 4 levels -- do those background levels 5 cause ovarian cancer? 6 MS. O'DELL: Objection to 7 the form. 8 THE WITNESS: The studies 9 that have been done by my 10 colleagues in the aftermath of the 11 World Trade Center disaster where 12 asbestos was generated have not at 13 this time -- and New York City 14 Public Health has not at this time 15 looked at ovarian cancer. Ovarian 16 cancer occurs within 10 to 30, up 17 to 40 years later. So since 9/11 18 was only 2001, there is -- there 19 is not sufficient time to have 20 developed ovarian cancer. 21 BY MR. HEGARTY: 22 Q. Doctor, before 9/11 there 23 were background levels of asbestos in 24 certain parts of New York City, correct?</p>
<p style="text-align: right;">Page 259</p> <p>1 a particle in air is, right? 2 A. Yes, sir, I do. 3 Q. Okay. And is it your 4 opinion that background levels of 5 asbestos in the air can cause ovarian 6 cancer? 7 MS. O'DELL: Objection to 8 form. 9 THE WITNESS: As I said, 10 sitting in this room, there should 11 not be any background level of 12 asbestos. So if you're talking 13 about background level in a 14 particular institute or industry 15 where they're developing it, those 16 levels are quite high, and yes, I 17 do believe that those levels 18 within a working environment can 19 indeed cause inflammation that can 20 lead to causation. 21 BY MR. HEGARTY: 22 Q. There are background levels 23 of asbestos in the air in New York City, 24 correct?</p>	<p style="text-align: right;">Page 261</p> <p>1 A. When there are houses that 2 were built with it. There is -- asbestos 3 is not just -- should not be -- unless 4 there's a source, asbestos should not -- 5 it would not be coming from jet engines. 6 It would not be coming from other 7 sources. If it's there, it came from a 8 specific source. It's like we should not 9 have lead in our body at all. But we do 10 because the lead came from the air where 11 there was lead in the gasoline. 12 So there shouldn't be 13 background levels of asbestos just 14 hanging around unless there's an adequate 15 source that produced it. 16 Q. Does EPA allow background 17 levels of asbestos in water? 18 A. I'm not familiar with that 19 information. That's in water. You asked 20 me about air. 21 Q. I asked you a different 22 question. I can ask you a different 23 question, Doctor. 24 A. I understand the question,</p>

<p style="text-align: right;">Page 262</p> <p>1 yes.</p> <p>2 Q. Does EPA allow background</p> <p>3 levels of asbestos in water?</p> <p>4 A. I have not reviewed that</p> <p>5 literature.</p> <p>6 Q. As a toxicologist, you agree</p> <p>7 that dose or level of exposure determines</p> <p>8 the toxicity of substances, correct?</p> <p>9 MS. O'DELL: Object to the</p> <p>10 form.</p> <p>11 THE WITNESS: I believe that</p> <p>12 dose as well as frequency,</p> <p>13 duration, time of exposure are</p> <p>14 all -- as well as dose contribute</p> <p>15 to the toxicity of an agent.</p> <p>16 BY MR. HEGARTY:</p> <p>17 Q. You agree that a substance</p> <p>18 can produce a harmful effect only if it</p> <p>19 reaches a susceptible biological system</p> <p>20 within the body in high enough</p> <p>21 concentration, correct?</p> <p>22 MS. O'DELL: Objection to</p> <p>23 form.</p> <p>24 THE WITNESS: It depends on</p>	<p style="text-align: right;">Page 264</p> <p>1 not been done.</p> <p>2 There are -- there is</p> <p>3 information on no observable</p> <p>4 adverse effect level that has been</p> <p>5 established using a dose-response</p> <p>6 by the NTP, National Toxicology</p> <p>7 Program.</p> <p>8 And two milligrams of talc</p> <p>9 that they used produced minimal --</p> <p>10 minimal affects in the rats and</p> <p>11 mice that they tested. So</p> <p>12 somewhere below at least, from an</p> <p>13 inhalation perspective, is --</p> <p>14 produces no effect.</p> <p>15 However, they saw effects</p> <p>16 even at the lowest, two milligrams</p> <p>17 per.</p> <p>18 BY MR. HEGARTY:</p> <p>19 Q. My question was specific to</p> <p>20 ovarian cancer. That study did not --</p> <p>21 did not identify any ovarian cancers in</p> <p>22 the mice -- in the mice or rats, correct?</p> <p>23 A. That's not what they looked</p> <p>24 for.</p>
<p style="text-align: right;">Page 263</p> <p>1 the -- let me read your question</p> <p>2 over. It was a lengthy question.</p> <p>3 It depends on the -- on the</p> <p>4 toxicant that you're talking</p> <p>5 about. There is dose that you're</p> <p>6 exposed to, or concentration that</p> <p>7 you're supposed to, and dose to</p> <p>8 the target tissue. And for every</p> <p>9 different -- every different</p> <p>10 chemical, there is a different</p> <p>11 target dose that could start a</p> <p>12 biological process.</p> <p>13 BY MR. HEGARTY:</p> <p>14 Q. And what is the target dose</p> <p>15 that is necessary to start the biologic</p> <p>16 process of talc and ovarian cancer?</p> <p>17 MS. O'DELL: Object to the</p> <p>18 form.</p> <p>19 THE WITNESS: Well, if</p> <p>20 you -- if you look at talc as a</p> <p>21 whole, to give you a</p> <p>22 concentration, a threshold</p> <p>23 concentration, I'm not sure that</p> <p>24 has been -- I don't -- that has</p>	<p style="text-align: right;">Page 265</p> <p>1 Q. My question is specific to</p> <p>2 ovarian cancer.</p> <p>3 A. Let me read your question</p> <p>4 over again. Could you repeat your</p> <p>5 question. It's already gone past.</p> <p>6 Q. What is the target dose that</p> <p>7 is necessary to start the biologic</p> <p>8 process of talc and ovarian cancer?</p> <p>9 A. Well, as I talked about, one</p> <p>10 fiber of asbestos could start the</p> <p>11 biological process. It is not clear if</p> <p>12 there is a threshold dose or a</p> <p>13 concentration, or whether one -- and</p> <p>14 we're talking about the whole talcum</p> <p>15 powder product. We're not talking about</p> <p>16 any one product. You're talking about</p> <p>17 the whole process and how much it will</p> <p>18 start the biological process.</p> <p>19 It's unknown, it's not in</p> <p>20 the literature. But I will tell you that</p> <p>21 even small doses that are used of the</p> <p>22 talcum -- of a talcum product, if you</p> <p>23 take a woman who takes a handful, if you</p> <p>24 take a woman that takes a little bit on a</p>

<p style="text-align: right;">Page 266</p> <p>1 powder puff, that amount could even, 2 depending upon the woman, the 3 susceptibility, the vulnerability, can 4 all start the process. 5 We're talking about the 6 process, in my opinion. What you're 7 talking about and in the opinion that I 8 report here, is that that can start an 9 inflammatory process. 10 Q. And what is the number of 11 particles of talc necessary to start the 12 biologic process? 13 MS. O'DELL: Object to form. 14 THE WITNESS: That is not in 15 the scientific literature. 16 BY MR. HEGARTY: 17 Q. Over Pages 6 through 8 of 18 your report you discuss asbestos. Is the 19 presence of asbestos in talc necessary 20 for your biologic plausibility opinions? 21 A. I looked at the entire 22 product. 23 Q. Well, do you intend to 24 testify that there is biologic</p>	<p style="text-align: right;">Page 268</p> <p>1 THE WITNESS: Can -- can you 2 address the question again? 3 BY MR. HEGARTY: 4 Q. Is it your opinion that pure 5 talc does not exist? 6 When I say pure talc, I mean 7 talc without asbestos, without heavy 8 metals, without fragrance. 9 MS. O'DELL: Objection to 10 form. 11 THE WITNESS: The idea of 12 talc is that it has, within its 13 lattice, metals. 14 So platy talc refers to the 15 structure or the morphology of the 16 talc, how it looks, what 17 dimensions it's in. 18 So, do I think there is 19 platy talc? Of course there is 20 platy talc. 21 BY MR. HEGARTY: 22 Q. Is there platy talc without 23 asbestos? 24 A. Well, according to the</p>
<p style="text-align: right;">Page 267</p> <p>1 plausibility between pure talc, the platy 2 talc, and ovarian cancer? 3 MS. O'DELL: Object to the 4 form. 5 THE WITNESS: I don't 6 think -- my opinion is that there 7 may not be anything such as platy 8 talc in a pure form. 9 BY MR. HEGARTY: 10 Q. Okay. It's your opinion 11 that pure talc does not exist? 12 MS. O'DELL: I'm not sure 13 she -- she finished her answer. 14 Had you finished, Doctor, 15 before? 16 THE WITNESS: I actually 17 need a little water. 18 MS. O'DELL: Okay. Sure. 19 Had you finished your answer 20 before the second question was 21 asked? 22 THE WITNESS: No. 23 MS. O'DELL: Okay. You may 24 finish.</p>	<p style="text-align: right;">Page 269</p> <p>1 studies out of Mossman's laboratories, 2 they used asbestos, they used talc that 3 contained nonfibrous talc. 4 Q. Do you have an opinion on 5 whether there is talc without asbestos? 6 MS. O'DELL: Object to the 7 form. 8 THE WITNESS: In many of the 9 documents from Johnson & Johnson, 10 they measured fibrous talc as well 11 as other forms, non-asbestiform, 12 and they -- they found that there 13 were samples, individual samples 14 that they reported as 15 nondetectable as having 16 asbestiform talc. 17 BY MR. HEGARTY: 18 Q. Well, do you have an opinion 19 of whether there is talc without 20 asbestos? 21 A. It depends where -- where 22 it's mined. If it's mined in an area 23 where people were extremely cautious, 24 there could be.</p>

<p style="text-align: right;">Page 270</p> <p>1 Q. Did you do analysis of 2 biologic plausibility for talc without 3 asbestos?</p> <p>4 MS. O'DELL: Objection to 5 form.</p> <p>6 THE WITNESS: My biological 7 assessment, my -- my biological 8 plausibility was looking at the 9 entire product of talcum powder.</p> <p>10 BY MR. HEGARTY:</p> <p>11 Q. And how do you define the 12 entire product?</p> <p>13 A. The entire product is 14 whatever are the ingredients or listed 15 within the documents or the test results 16 from Imerys that -- that indicate what 17 they measured, including the metals, the 18 asbestos, the -- the asbestiform fibers, 19 the fragrances.</p> <p>20 Q. So you did your biologic 21 plausibility analysis with -- based on 22 talc that has asbestos, heavy metals and 23 fragrance in it, correct?</p> <p>24 MS. O'DELL: Objection to</p>	<p style="text-align: right;">Page 272</p> <p>1 sure how that would be done or I 2 don't think it could be done.</p> <p>3 What I did was I did it for 4 the entire product.</p> <p>5 BY MR. HEGARTY:</p> <p>6 Q. And what do you -- what do 7 you think -- what is your opinion -- 8 strike that.</p> <p>9 What is in the entire 10 product in your opinion?</p> <p>11 A. Based upon the Johnson & 12 Johnson documents. That's where my -- 13 that's where I will tell you what is in 14 there.</p> <p>15 As -- as far as the product 16 documents, it indicates that there are 17 metals, including -- not -- not totally 18 inclusive of, but to mention a few of the 19 more well-known ones, cobalt, chromium 20 and nickel.</p> <p>21 There are also, according to 22 the Crowley report, there are also many 23 chemicals that make up a fragrance. And 24 there -- and in many of the samples</p>
<p style="text-align: right;">Page 271</p> <p>1 form.</p> <p>2 THE WITNESS: I did my 3 biological plausibility on talcum 4 powder products.</p> <p>5 I looked at individual 6 products, individual constituents 7 in adding to my -- to my report, 8 to my document. But I looked at 9 the entire product. And it is my 10 opinion that the entire product 11 causes inflammation and that 12 inflammation then goes on as a 13 triggering mechanism to turn on 14 certain genes and to bind iron 15 that can lead to the changes 16 needed for cancer in the ovary.</p> <p>17 BY MR. HEGARTY:</p> <p>18 Q. You did not do a separate 19 analysis of talc without asbestos or 20 without -- and without heavy metals and 21 without fragrance, correct?</p> <p>22 MS. O'DELL: Object to the 23 form.</p> <p>24 THE WITNESS: I'm not even</p>	<p style="text-align: right;">Page 273</p> <p>1 tested, there was asbestos or asbestiform 2 fibers, some of which were called fibrous 3 talc, others were called asbestiform and 4 others in which they were called asbestos 5 fibers, or amphiboles or anthophyllite.</p> <p>6 Q. Did you review all the 7 test --</p> <p>8 A. Anthophyllite.</p> <p>9 Q. I'm sorry.</p> <p>10 Did you review all the 11 testing documents produced by Johnson & 12 Johnson and Imerys in this case?</p> <p>13 A. I reviewed the documents 14 that are in the production document black 15 binder to my right.</p> <p>16 Q. Those were provided to you 17 by plaintiffs' counsel, correct?</p> <p>18 A. That is correct.</p> <p>19 Q. Did you ask them if they 20 provided to you all testing documents 21 that had been produced in this case with 22 regard -- by Johnson & Johnson and 23 Imerys?</p> <p>24 A. I did not ask that question</p>

<p style="text-align: right;">Page 274</p> <p>1 specifically.</p> <p>2 Q. Do you know whether there</p> <p>3 are additional documents of tests --</p> <p>4 documents describing tests that were done</p> <p>5 by Johnson & Johnson and/or Imerys with</p> <p>6 regard to asbestos, heavy metals,</p> <p>7 fragrances and talc?</p> <p>8 MS. O'DELL: Object to form.</p> <p>9 THE WITNESS: Plaintiff</p> <p>10 counsels and myself did talk about</p> <p>11 that, some of that information,</p> <p>12 and --</p> <p>13 MS. O'DELL: Doctor,</p> <p>14 don't -- in terms of our</p> <p>15 conversations --</p> <p>16 THE WITNESS: I'm sorry.</p> <p>17 MS. O'DELL: -- those</p> <p>18 conversations are our work</p> <p>19 product.</p> <p>20 But to the degree that your</p> <p>21 answer doesn't depend on our</p> <p>22 conversations, you may -- you may</p> <p>23 answer.</p> <p>24 THE WITNESS: I -- I made it</p>	<p style="text-align: right;">Page 276</p> <p>1 not present.</p> <p>2 Q. You relied on plaintiffs'</p> <p>3 counsel to select for you the testing</p> <p>4 documents that you reviewed, correct?</p> <p>5 A. I -- I read and reviewed</p> <p>6 whatever they sent me.</p> <p>7 Q. And did you do anything to</p> <p>8 verify that you had all the documents</p> <p>9 regarding the testing of Johnson's Baby</p> <p>10 Powder?</p> <p>11 A. I did nothing personally</p> <p>12 other than ask the -- the attorneys if</p> <p>13 there was anything else I needed in</p> <p>14 forming my opinion. In -- of production</p> <p>15 documents, if we're just referring to</p> <p>16 that.</p> <p>17 I have no access to</p> <p>18 production documents on my own or through</p> <p>19 the internet. And I know none of the</p> <p>20 other deposeses.</p> <p>21 Q. Did you do a comparison of</p> <p>22 biologic plausibility across various</p> <p>23 brands of talcum powder products?</p> <p>24 A. I did not personally do any</p>
<p style="text-align: right;">Page 275</p> <p>1 clear that I would like to see</p> <p>2 documents that could go into my</p> <p>3 assessment of biological</p> <p>4 plausibility.</p> <p>5 BY MR. HEGARTY:</p> <p>6 Q. Would you like to see</p> <p>7 documents showing that there is no</p> <p>8 asbestos in talcum powder, in particular</p> <p>9 Johnson's Baby Powder?</p> <p>10 A. I will review any documents</p> <p>11 that are provided to me, if asked to</p> <p>12 review them.</p> <p>13 Q. Did you ask plaintiffs'</p> <p>14 counsel to provide you documents of</p> <p>15 testing showing no asbestos in Johnson's</p> <p>16 Baby Powder?</p> <p>17 A. Many of those -- of the</p> <p>18 documents that are in the product</p> <p>19 production document show that there are</p> <p>20 samples that do not contain asbestos, or</p> <p>21 I will say asbestiform or talc fibers.</p> <p>22 So there is information in there showing</p> <p>23 when there is -- it is present and</p> <p>24 information in there showing when it was</p>	<p style="text-align: right;">Page 277</p> <p>1 of that. However many of the documents</p> <p>2 and many of the studies including the</p> <p>3 Longo supplement did compare, for</p> <p>4 example, I think I misspoke when I said</p> <p>5 one of the places that Johnson & Johnson</p> <p>6 gets their talc is Korea. What I meant</p> <p>7 was China. I should have said Asia. So</p> <p>8 Korea is also a mine that provided, but</p> <p>9 not to Johnson & Johnson.</p> <p>10 MS. O'DELL: Hey, Mark,</p> <p>11 we've been going about an hour and</p> <p>12 15 minutes.</p> <p>13 MR. HEGARTY: Okay.</p> <p>14 MS. O'DELL: Can we take a</p> <p>15 break?</p> <p>16 MR. HEGARTY: Yeah.</p> <p>17 THE VIDEOGRAPHER: The time</p> <p>18 is 2:27 p.m. Off the record.</p> <p>19 (Short break.)</p> <p>20 THE VIDEOGRAPHER: We are</p> <p>21 back on the record. The time is</p> <p>22 2:45 p.m.</p> <p>23 BY MR. HEGARTY:</p> <p>24 Q. Doctor, if evidence was that</p>

<p style="text-align: right;">Page 278</p> <p>1 there is no asbestos in Johnson's Baby 2 Powder, would that change your opinions 3 as to biological plausibility? 4 A. No, sir, it would not. 5 Q. Same question with regard to 6 heavy metals. If there were no heavy 7 metals in Johnson's Baby Powder, would 8 that change your opinions on biological 9 plausibility? 10 A. I looked at the entire 11 product and it would not -- it would not 12 change my opinion, as it exists 13 currently, with biological plausibility 14 that it would cause ovarian cancer 15 through -- through inflammation, is my 16 opinion. 17 Q. In looking at your heavy 18 metals section, beginning at Page 8 of 19 your report -- are you there? 20 A. I'm not. I had to put my 21 glasses on. Thank you. 22 Q. There are no studies that 23 have looked at the effects of these 24 metals in powder dusted on the perineum,</p>	<p style="text-align: right;">Page 280</p> <p>1 ludicrous actually. 2 Q. None of the studies that you 3 cite in your heavy metals section link 4 the exposures that you discussed to 5 ovarian cancer risk, correct? 6 THE WITNESS: I'm sorry. 7 This is not coming up. 8 (Whereupon, a discussion was 9 held off the stenographic record.) 10 THE WITNESS: They -- the 11 studies that I list for the 12 individual metals talk about the 13 potential inflammatory and 14 carcinogenic potential of those 15 particular metals. And based on 16 the Crowley report, there are, and 17 other production documents from 18 Johnson & Johnson, they list three 19 particular metals that are 20 associated with Johnson & Johnson 21 products, cobalt, nickel and 22 chromium. 23 BY MR. HEGARTY: 24 Q. That was not my question.</p>
<p style="text-align: right;">Page 279</p> <p>1 correct? 2 A. Your question is there are 3 no studies looking at these individual 4 metals? 5 Q. Correct? 6 A. Perineal studies in the 7 ovarian -- 8 Q. No, my question is, there 9 are no studies that looked at the effects 10 of these metals in powder dusted on the 11 perineum, correct? 12 A. I'm not sure I understand 13 your question. 14 Q. You don't cite any studies 15 that have looked at the effect of 16 applying these metals to the perineum, 17 correct? 18 A. To my knowledge, there are 19 no specific animal studies that show 20 nickel was applied to the perineal. 21 Q. There are no human studies 22 either, correct? 23 A. To my knowledge, there are 24 no human studies. That would be</p>	<p style="text-align: right;">Page 281</p> <p>1 My question is, none of the studies that 2 you cite -- 3 A. On the -- 4 Q. -- in your section on heavy 5 metals, evaluate ovarian carcinogenicity 6 potentials of these metals, correct? 7 MS. O'DELL: Object to the 8 form. 9 THE WITNESS: I do not talk 10 about ovarian cancer in particular 11 relation to these three metals 12 that I cited -- 13 BY MR. HEGARTY: 14 Q. No studies -- 15 A. -- in the report. 16 Q. -- that you cite refer to 17 risk of ovarian cancer with exposure to 18 these metals, correct? 19 A. With my charge being 20 biological plausibility, I thought that 21 it was my opinion -- my professional 22 opinion is that it was more important to 23 discuss the potential for inflammatory 24 responsiveness and carcinogenic</p>

<p style="text-align: right;">Page 282</p> <p>1 potential.</p> <p>2 Q. Doctor, you don't cite any</p> <p>3 studies that look at -- look at the</p> <p>4 ovarian carcinogenicity potential of any</p> <p>5 of these metals, correct?</p> <p>6 MS. O'DELL: Object to form.</p> <p>7 THE WITNESS: Not in my</p> <p>8 report.</p> <p>9 BY MR. HEGARTY:</p> <p>10 Q. What are the exposure levels</p> <p>11 of these metals necessary to have</p> <p>12 biologic plausibility of ovarian cancer?</p> <p>13 A. As far as biological</p> <p>14 plausibility of these metals, these</p> <p>15 metals are -- unless there are particular</p> <p>16 standards for a particular metal, nothing</p> <p>17 is really established for what it would</p> <p>18 take for nickel to cause ovarian cancer.</p> <p>19 However, the ability of</p> <p>20 these metals to produce inflammation are</p> <p>21 very, very low levels. And if they</p> <p>22 produce inflammation, then they have the</p> <p>23 potential to go on to produce cancer.</p> <p>24 And many of these metals do.</p>	<p style="text-align: right;">Page 284</p> <p>1 them.</p> <p>2 Q. Did you find any?</p> <p>3 A. Again, the purpose of</p> <p>4 writing this section on heavy metals had</p> <p>5 to do with bringing out the inflammatory</p> <p>6 and the biological plausibility that in</p> <p>7 my mind is linked to talc and ovarian</p> <p>8 cancer.</p> <p>9 Q. Doctor, listen to my</p> <p>10 question. Did you find any studies</p> <p>11 reporting on a risk of ovarian cancer</p> <p>12 with exposure to any of those metals?</p> <p>13 MS. O'DELL: Objection to</p> <p>14 form.</p> <p>15 THE WITNESS: I found in</p> <p>16 cobalt, but it does not have to do</p> <p>17 with ovarian cancer, but I did</p> <p>18 find that the absorption of cobalt</p> <p>19 is much higher in women than in</p> <p>20 men. And that many of these</p> <p>21 studies show that you have</p> <p>22 increased proliferation. And as I</p> <p>23 said, mine was -- my question that</p> <p>24 I needed to address was biological</p>
<p style="text-align: right;">Page 283</p> <p>1 Q. Well, none of these studies</p> <p>2 report a threshold level of exposure to</p> <p>3 cobalt, chromium, or nickel to increase</p> <p>4 the risk of ovarian cancer, correct?</p> <p>5 MS. O'DELL: Object to the</p> <p>6 form.</p> <p>7 THE WITNESS: That was not</p> <p>8 the purpose of my writing.</p> <p>9 My -- my writing was to</p> <p>10 exemplify the carcinogenic</p> <p>11 potential and the inflammatory and</p> <p>12 some of the human health effects</p> <p>13 that are commonly seen. Ovarian</p> <p>14 cancer is not that common. And so</p> <p>15 it's not unusual that other --</p> <p>16 that ovarian cancer was not looked</p> <p>17 into in some of these studies.</p> <p>18 BY MR. HEGARTY:</p> <p>19 Q. Well, you found no studies</p> <p>20 looking at exposure to any of those</p> <p>21 metals and risk of ovarian cancer,</p> <p>22 correct?</p> <p>23 A. It's not that I didn't find</p> <p>24 any. I wasn't particularly looking for</p>	<p style="text-align: right;">Page 285</p> <p>1 plausibility.</p> <p>2 So I did find many of these</p> <p>3 factors, many of these metals, all</p> <p>4 of these metals have the potential</p> <p>5 to produce the changes that are in</p> <p>6 the carcinogenic process.</p> <p>7 BY MR. HEGARTY:</p> <p>8 Q. I'm going to ask the</p> <p>9 question one more time. And if we don't</p> <p>10 get an answer I'm going to call Judge</p> <p>11 Pisano.</p> <p>12 Cite for me, which study did</p> <p>13 you find that linked exposure to these</p> <p>14 metals to ovarian cancer?</p> <p>15 MS. O'DELL: Objection to</p> <p>16 the form.</p> <p>17 Dr. Zelikoff has answered</p> <p>18 your question multiple times.</p> <p>19 But you may answer it again.</p> <p>20 BY MR. HEGARTY:</p> <p>21 Q. Let me ask it differently.</p> <p>22 Did you find any studies reporting on a</p> <p>23 risk of ovarian cancer with exposure to</p> <p>24 any of these metals, that being cobalt,</p>

<p style="text-align: right;">Page 286</p> <p>1 chromium, or nickel?</p> <p>2 A. I was not looking</p> <p>3 specifically for that. So, no, I did not</p> <p>4 find that.</p> <p>5 Q. Which of the studies that</p> <p>6 you report show that the exposure levels</p> <p>7 evaluated in those studies are in any way</p> <p>8 related to human exposure levels through</p> <p>9 Johnson's Baby Powder?</p> <p>10 MS. O'DELL: Object to the</p> <p>11 form.</p> <p>12 THE WITNESS: Are you</p> <p>13 talking about inhalation or</p> <p>14 perineal application?</p> <p>15 BY MR. HEGARTY:</p> <p>16 Q. Either method of exposure.</p> <p>17 A. So many of the inhalation</p> <p>18 numbers are concentrations, and looking</p> <p>19 at the Johnson & Johnson documents in</p> <p>20 terms of what is in the head and in the</p> <p>21 face area after diapering as well as</p> <p>22 during powdering, indicates that the</p> <p>23 concentrations that are possibly inhaled</p> <p>24 contain particles that can initiate a</p>	<p style="text-align: right;">Page 288</p> <p>1 of these metals in terms of parts</p> <p>2 per million, whatever talc reached</p> <p>3 there, there's -- there is a</p> <p>4 strong potential that that amount</p> <p>5 of the concentration of the metal</p> <p>6 would also reach the target organ.</p> <p>7 BY MR. HEGARTY:</p> <p>8 Q. That's not my question,</p> <p>9 Doctor.</p> <p>10 How much nickel, cobalt and</p> <p>11 chromium reached the ovary with a single</p> <p>12 application of Johnson's Baby Powder to</p> <p>13 the perineum?</p> <p>14 A. I don't have -- that</p> <p>15 information is not available.</p> <p>16 They did show in studies, in</p> <p>17 a few studies, I think it was the</p> <p>18 Hamilton study that -- or Henderson</p> <p>19 study -- that there -- talc indeed does</p> <p>20 reach the ovary from perineal application</p> <p>21 or from intravaginal application. And</p> <p>22 whatever is -- whatever the concentration</p> <p>23 is that reached the ovary, carried with</p> <p>24 it these -- one -- one or more or all of</p>
<p style="text-align: right;">Page 287</p> <p>1 response.</p> <p>2 Also, from looking at the</p> <p>3 Johnson & Johnson documents, many of</p> <p>4 those results indicate -- and I think we</p> <p>5 have an exhibit here of the table of the</p> <p>6 concentrations that were found.</p> <p>7 Well, it's not at my local</p> <p>8 fingertips here. But --</p> <p>9 MS. O'DELL: Are you looking</p> <p>10 for Exhibit C, Doctor, I think</p> <p>11 it's right there with -- on</p> <p>12 your -- on your paper clip.</p> <p>13 MR. HEGARTY: Let me</p> <p>14 withdraw the question.</p> <p>15 BY MR. HEGARTY:</p> <p>16 Q. Doctor, how much nickel,</p> <p>17 cobalt and chromium reach the ovary with</p> <p>18 one application of Johnson's Baby Powder</p> <p>19 to the perineum?</p> <p>20 MS. O'DELL: Object to the</p> <p>21 form.</p> <p>22 THE WITNESS: Since much of</p> <p>23 the -- since Johnson's Baby Powder</p> <p>24 has a high concentrations of some</p>	<p style="text-align: right;">Page 289</p> <p>1 these three metals.</p> <p>2 Q. You agree --</p> <p>3 A. So it was a similar</p> <p>4 concentration.</p> <p>5 Q. You agree that all of the</p> <p>6 metals you talk about are in -- are all</p> <p>7 around us, they are in food, correct?</p> <p>8 A. The metals nickel, chromium,</p> <p>9 cobalt can be in food, yes.</p> <p>10 Q. They are in the air,</p> <p>11 correct?</p> <p>12 A. They are in certain ambient</p> <p>13 environments.</p> <p>14 Q. These are metals that are</p> <p>15 considered ubiquitous, correct?</p> <p>16 MS. O'DELL: Objection to</p> <p>17 the form.</p> <p>18 THE WITNESS: They are --</p> <p>19 chromium not as much -- I'm sorry,</p> <p>20 cobalt not as much. But chromium</p> <p>21 and nickel, they are in the air,</p> <p>22 and depending upon the environment</p> <p>23 that is producing it, if you go to</p> <p>24 Sundre, Canada, you can have lots</p>

<p style="text-align: right;">Page 290</p> <p>1 of nickel in the air. But if you 2 go to New York City, concentrate 3 as we've measured in my laboratory 4 prior to this deposition, or prior 5 to this case, my involvement in 6 this case, you will see very small 7 concentrations of nickel. There 8 should not be a lot in the air. 9 And we also measured 10 chromium, and it should not be -- 11 unless you have a polluted 12 environment there should not be a 13 lot of these metals in the air. 14 BY MR. HEGARTY: 15 Q. Is the metal are not -- the 16 metals that are in the air, nickel and 17 chromium, sufficient to have biologic 18 plausibility between those metals and 19 ovarian cancer? 20 A. Those -- those metals, yes, 21 the metals in the air can cause an 22 inflammatory response. The 23 concentrations of the metals in the air 24 can cause an inflammatory response and</p>	<p style="text-align: right;">Page 292</p> <p>1 Q. Did you do an analysis 2 yourself of Johnson's Baby Powder for the 3 presence of these heavy metals? 4 A. I did not do any 5 instrumentation studies measuring the 6 amount. I -- I relied on the documents. 7 Q. But you are capable of doing 8 that analysis, correct? 9 A. We are capable, in my 10 laboratory, along with colleagues, of 11 measuring by XRF, x-ray fluorescence, and 12 by ICP mass spec, measuring the amounts 13 of metals in tissues, correct. 14 Q. But you did not do that 15 testing here, correct? 16 A. My job was to define 17 biological plausibility based upon 18 literature, relevant literature and 19 documents, internal documents. 20 Q. Nowhere in your report do 21 you identify the exposure levels of any 22 of these metals that are necessary to 23 cause ovarian cancer, correct? 24 MS. O'DELL: Objection to</p>
<p style="text-align: right;">Page 291</p> <p>1 can start processes and change gene 2 expression within cells. 3 Q. Cite for me any study that 4 shows that inflammatory response has ever 5 occurred in the ovary. 6 MS. O'DELL: Objection to 7 form. 8 THE WITNESS: There are 9 granulomas that have been found in 10 animal studies of -- in the lung. 11 You are talking about in the 12 ovary, I understand that. 13 BY MR. HEGARTY: 14 Q. I'm talking about the 15 studies that have not looked at talc, but 16 have looked at cobalt, chromium -- 17 A. Okay. 18 Q. -- nickel and cobalt without 19 regard to talc, cite for me any studies 20 that have shown that those metals have 21 caused inflammation in the ovary? 22 A. By themselves, there are no 23 studies that demonstrate that, that I'm 24 aware of.</p>	<p style="text-align: right;">Page 293</p> <p>1 form. Asked and answered. 2 THE WITNESS: There is no 3 literature that says you need one 4 particle or ten particles. 5 The inflammatory response 6 that nickel causes is extremely 7 well established, even at very low 8 concentrations. And -- and the 9 same is true for hexavalent 10 chromium and for chromium, 11 trivalent chromium. 12 BY MR. HEGARTY: 13 Q. Are there any studies that 14 report on exposure of these metals to the 15 ovaries? 16 A. Are you talking about alone? 17 Q. Individually or together, 18 but the metals themselves. 19 A. Just the metals -- 20 MS. O'DELL: Object -- 21 objection to form. 22 THE WITNESS: These metals 23 by themselves have been tested 24 extensively in cells and in -- in</p>

<p style="text-align: right;">Page 294</p> <p>1 animals to produce inflammation, 2 to change the epigenome of the 3 cells, to change gene expression. 4 And there was no -- there was no 5 reason to believe whether or not 6 there are specific studies 7 associated with the ovary. There 8 are no reason to believe that it 9 would not do the same effects in 10 cells as well as in the ovary, in 11 the lung, and the kidney and the 12 liver. 13 BY MR. HEGARTY: 14 Q. Doctor, you are not aware of 15 any studies that have looked at the 16 effects of these metals on human ovarian 17 cells, correct? 18 MS. O'DELL: Object to the 19 form. 20 THE WITNESS: Again, I'm not 21 an epidemiologist, so -- and I'm 22 not a clinical toxicologist. So I 23 will have to stand by the -- the 24 data that I do know in -- in</p>	<p style="text-align: right;">Page 296</p> <p>1 form. 2 THE WITNESS: The exposures 3 are similar, or can be similar. 4 But as I stated before, for 5 these metals as well as for 6 asbestiform fibers, all it takes 7 is a small amount, if not just one 8 fiber, to cause the response and 9 to start the process of 10 inflammation, gene expression, 11 upregulation of genes that are 12 associated with biological 13 mediators, proinflammatory 14 cytokines. 15 BY MR. HEGARTY: 16 Q. Yet you cite no study that 17 reports that response in human ovarian 18 cells, correct? 19 MS. O'DELL: Object to the 20 form. 21 THE WITNESS: I -- if you're 22 still talking about individual 23 metals, no. 24 But if you're talking about</p>
<p style="text-align: right;">Page 295</p> <p>1 extensive -- have extensive 2 knowledge of. And that's human ex 3 vivo and in vitro studies. And I 4 am not aware. 5 That is not to say that they 6 are not out there. And I 7 especially do not know about the 8 humans, because I focus as a 9 toxicologist. I'm an animal 10 toxicologist. 11 BY MR. HEGARTY: 12 Q. Did you do any comparison 13 between the doses of -- of the metals 14 reported in the studies that you cited to 15 those in women using talc? 16 A. I did no calculations on -- 17 on my own. 18 Q. Did you do any calculations 19 that tested these metals in animals to 20 determine what the -- that -- that they 21 relate in any way to the dose that a 22 human would experience through Johnson's 23 Baby Powder use? 24 MS. O'DELL: Objection to</p>	<p style="text-align: right;">Page 297</p> <p>1 in vitro studies like those of 2 Saed who looked for oxidative 3 stress and -- and prooxidant 4 changes, and if you are talking 5 about Shukla study who also looked 6 at ovarian cells, human ovarian 7 cells, and looked at changes in 8 gene expression associated with 9 oxidant production and reactive 10 oxygen species production, then 11 yes, in cell culture using human 12 ovarian epithelial cells, because 13 that's what we are talking about 14 here. 15 BY MR. HEGARTY: 16 Q. None of those studies 17 applied nickel to human ovarian cells, 18 did they? 19 A. No, they did not. 20 Q. None of those studies 21 applied cobalt to human ovarian cells, 22 correct? 23 A. No, they did not. 24 Q. None of those studies</p>

<p style="text-align: right;">Page 298</p> <p>1 applied chromium to ovarian -- human 2 ovarian cells, correct? 3 A. Correct. But what we're 4 talk -- what I'm talking about and the 5 basis of my opinion is the product in its 6 entirety, not breaking it down to 7 individual constituents. 8 Q. Is it necessary for purposes 9 of your biologic plausibility opinion 10 that talc reach the ovary? 11 A. Not necessarily. 12 Talc does -- talc and any 13 other particle does not have to reach the 14 site of deposition. They can, and -- and 15 do, I believe that they not only migrate 16 to an area and they can get to an area 17 and then cause inflammation which then 18 can be -- the cytokines where there's 19 tumor necrosis factor, interleukin-1, or 20 any of the other proinflammatory 21 cytokines can then get to the air, the 22 site of this -- this target organ. 23 So you do not have to have, 24 in particle toxicology and in talc</p>	<p style="text-align: right;">Page 300</p> <p>1 target site, let's say in the case 2 of inhalation or in the case of 3 direct application to the perineal 4 area, you will have the process of 5 impacting with those cells and 6 generating cell mediated reactions 7 and immunological reactions and 8 inflammatory responses. 9 And those inflammatory 10 responses and those reactive 11 oxygen species, except for 12 hydrogen peroxide which can't 13 travel a far distance, can get 14 into -- can and do get into the 15 blood circulation and then can 16 reach distant organs. 17 BY MR. HEGARTY: 18 Q. Cite for me any published 19 authority that says that inflammation in 20 the lungs will cause inflammation in the 21 ovaries. 22 MS. O'DELL: Object to the 23 form. Misstates her testimony. 24 THE WITNESS: To that</p>
<p style="text-align: right;">Page 299</p> <p>1 toxicology, you do not have to have the 2 presence. Although, in early studies 3 they have found talc particles not only 4 in the ovary, but also in the lymph 5 node -- in the lymphatics that drain the 6 ovary. 7 Q. Cite for me any study that 8 has reported inflammation in the ovaries 9 from inflammation of -- due to a particle 10 in the lung -- strike that. 11 Is it your contention that 12 inflammation in the lung due to a 13 particle will cause inflammation in the 14 ovaries? 15 MS. O'DELL: Objection to 16 form. 17 THE WITNESS: I'm telling 18 you that -- 19 MS. O'DELL: Go ahead. 20 THE WITNESS: -- there's 21 biological plausibility to suggest 22 that. 23 When you have a particle 24 coming in and going to a local</p>	<p style="text-align: right;">Page 301</p> <p>1 specific question, no. But I 2 can -- I can cite you many studies 3 that show in terms of other 4 particles for the lungs that has 5 been shown to cause inflammation 6 in other areas. 7 For example, in the case of 8 Ghio and other investigators, you 9 will find inflammation not only in 10 the blood by the measurement of 11 cytokines in the blood, even 12 though the first target organ was 13 the -- was the lungs. 14 Also, if you look at 15 obesity, obesity is a pro-oxidant 16 state, and that can generate -- 17 the reason obesity causes other 18 health effects is because it's a 19 big mass of inflammation. And the 20 inflammation in that particular 21 site of all those fatty cells, 22 they can release inflammatory 23 mediators that go all over. And 24 that literature is out there.</p>

<p style="text-align: right;">Page 302</p> <p>1 BY MR. HEGARTY:</p> <p>2 Q. So is it your opinion for</p> <p>3 purposes of your biological</p> <p>4 plausibility -- strike that.</p> <p>5 Is it -- is your biological</p> <p>6 plausibility opinion that talc inhaled</p> <p>7 and in the lungs causes inflammation in</p> <p>8 the ovaries that can lead to ovarian</p> <p>9 cancer?</p> <p>10 A. There's plausibility for</p> <p>11 that, yes.</p> <p>12 Q. And can you cite for me any</p> <p>13 published authority that says that talc</p> <p>14 inhaled in the lungs will cause</p> <p>15 inflammation in the ovaries that can lead</p> <p>16 to ovarian cancer?</p> <p>17 A. There's multiple parts of</p> <p>18 that question.</p> <p>19 Q. That's a very specific</p> <p>20 question to that very specific subject</p> <p>21 area. Can you cite to me any published</p> <p>22 literature that says that?</p> <p>23 MS. O'DELL: Would you mind</p> <p>24 repeating the full question or</p>	<p style="text-align: right;">Page 304</p> <p>1 cadmium.</p> <p>2 Q. So in other words a lot of</p> <p>3 particles besides talc, according to you,</p> <p>4 can cause inflammation of the lungs,</p> <p>5 correct?</p> <p>6 A. Many do. There are others</p> <p>7 that do not, like titanium dioxide which</p> <p>8 were used in many studies as a control.</p> <p>9 Q. And those nanoparticles,</p> <p>10 those air particles --</p> <p>11 A. In fact --</p> <p>12 Q. -- those diesel particles.</p> <p>13 A. I'm sorry.</p> <p>14 Q. Okay. And those</p> <p>15 nanoparticles, those diesel particles,</p> <p>16 air particles that can cause inflammation</p> <p>17 in the lungs, will also cause</p> <p>18 inflammation in the ovaries, correct?</p> <p>19 MS. O'DELL: Objection to</p> <p>20 form.</p> <p>21 THE WITNESS: I said they</p> <p>22 will cause inflammation</p> <p>23 systemically. I did not indicate</p> <p>24 the ovaries.</p>
<p style="text-align: right;">Page 303</p> <p>1 read it.</p> <p>2 THE WITNESS: Any published</p> <p>3 authority that says that -- that</p> <p>4 says that talc inhaled in the</p> <p>5 lungs will cause inflammation in</p> <p>6 the ovaries that can lead to</p> <p>7 ovarian cancer.</p> <p>8 For that particular, and</p> <p>9 that specific of a question, I</p> <p>10 cannot cite you.</p> <p>11 BY MR. HEGARTY:</p> <p>12 Q. You have published</p> <p>13 extensively on particulates in the air</p> <p>14 causing inflammation in the lungs,</p> <p>15 correct?</p> <p>16 A. In the lungs and</p> <p>17 systemically.</p> <p>18 Q. And those particulates</p> <p>19 include?</p> <p>20 A. Air particulates;</p> <p>21 particulate matter, called PM, ambient</p> <p>22 PM; diesel exhaust particles. I'm also</p> <p>23 going to go to my CV. Nanoparticles,</p> <p>24 metal nanoparticles, specifically</p>	<p style="text-align: right;">Page 305</p> <p>1 BY MR. HEGARTY:</p> <p>2 Q. Well, there's no -- there's</p> <p>3 nothing unique about talc particles</p> <p>4 versus the other particles you mentioned,</p> <p>5 correct?</p> <p>6 MS. O'DELL: Object to form.</p> <p>7 THE WITNESS: Size, chemical</p> <p>8 composition, they -- they --</p> <p>9 particles -- particles are -- they</p> <p>10 can -- they can be different and</p> <p>11 they can be the same. So many</p> <p>12 studies use model particles to</p> <p>13 look at a negative effect like in</p> <p>14 the Shukla study where they used</p> <p>15 titanium dioxide particles of a</p> <p>16 similar size in their -- as a</p> <p>17 control and got no gene expression</p> <p>18 changes.</p> <p>19 Particles in the air, if</p> <p>20 you're looking at -- there are</p> <p>21 many factors that go into how a</p> <p>22 particle behaves, including size,</p> <p>23 including composition, including</p> <p>24 morphology.</p>

<p style="text-align: right;">Page 306</p> <p>1 BY MR. HEGARTY:</p> <p>2 Q. Well, by your methodology,</p> <p>3 any particle inhaled that causes</p> <p>4 inflammation in the lungs is biologically</p> <p>5 plausible, can lead to ovarian cancer,</p> <p>6 correct?</p> <p>7 MS. O'DELL: Object to form.</p> <p>8 THE WITNESS: No, it can --</p> <p>9 sorry. It can lead to</p> <p>10 inflammation systemically.</p> <p>11 BY MR. HEGARTY:</p> <p>12 Q. That can lead to ovarian</p> <p>13 cancer, correct?</p> <p>14 A. Inflammation --</p> <p>15 MS. O'DELL: Object to the</p> <p>16 form.</p> <p>17 Go ahead.</p> <p>18 THE WITNESS: Sorry.</p> <p>19 MS. O'DELL: Sorry.</p> <p>20 THE WITNESS: Inflammation</p> <p>21 is responsible for -- in my</p> <p>22 opinion, is the underlying</p> <p>23 mechanism, a key underlying</p> <p>24 mechanism for the association for</p>	<p style="text-align: right;">Page 308</p> <p>1 same inflammation that you believe that</p> <p>2 talc does, correct?</p> <p>3 A. Inflammation is</p> <p>4 characterized by certain key components.</p> <p>5 Inflammation -- whether it's an</p> <p>6 inflammation in the ovary or an</p> <p>7 inflammation in the lung or inflammation</p> <p>8 in the kidney, inflammation is an immune</p> <p>9 response. And it's going to involve key</p> <p>10 cells, including the macrophage, the</p> <p>11 neutrophil, the natural killer cell, all</p> <p>12 of which can produce reactive oxygen</p> <p>13 species -- well, primarily the</p> <p>14 macrophages and neutrophils produce</p> <p>15 oxygen radicals.</p> <p>16 However, the natural killer</p> <p>17 cell, they all produce cytokines, which</p> <p>18 can produce inflammation. So</p> <p>19 inflammation is characterized by the same</p> <p>20 components.</p> <p>21 Q. And you can't cite for me</p> <p>22 any different components of the</p> <p>23 inflammation caused by cadmium as you</p> <p>24 believe the inflammation that is caused</p>
<p style="text-align: right;">Page 307</p> <p>1 ovarian cancer, yes.</p> <p>2 BY MR. HEGARTY:</p> <p>3 Q. And that mechanism can be</p> <p>4 initiated by any particle inhaled into</p> <p>5 the lungs, correct?</p> <p>6 A. No, it's --</p> <p>7 MS. O'DELL: Objection to</p> <p>8 form.</p> <p>9 THE WITNESS: Sorry.</p> <p>10 Well, as -- again, as I</p> <p>11 stated, it depends on the -- it</p> <p>12 depends on the particle. For</p> <p>13 example, titanium dioxide will not</p> <p>14 produce inflammation in the lungs.</p> <p>15 However, other particles, many</p> <p>16 other particles, including</p> <p>17 cadmium, cadmium oxide particles</p> <p>18 do cause inflammation, as well as</p> <p>19 asbestos does, as well as talc has</p> <p>20 been shown to.</p> <p>21 They can all produce</p> <p>22 inflammation or oxidative stress.</p> <p>23 BY MR. HEGARTY:</p> <p>24 Q. Cadmium particles induce the</p>	<p style="text-align: right;">Page 309</p> <p>1 by talc, correct?</p> <p>2 A. When I measured inflammatory</p> <p>3 responses to the inhalation of cadmium</p> <p>4 nanoparticles, I looked for the standard</p> <p>5 inflammatory markers. So I measured in</p> <p>6 the lung and in the circulation. I</p> <p>7 measured the percentages of neutrophils,</p> <p>8 which is a key indicator, key criteria</p> <p>9 for inflammation. I determined</p> <p>10 macrophage numbers as well as function in</p> <p>11 terms of their ability to phagocytose, in</p> <p>12 their ability to produce reactive oxygen</p> <p>13 species. And I looked for lung injury,</p> <p>14 as measured by lactose, lactate</p> <p>15 dehydrogenase.</p> <p>16 So when one looks for</p> <p>17 inflammation in the body, whether it's an</p> <p>18 animal or a human, C-reactive protein,</p> <p>19 you are going to be looking for all the</p> <p>20 same markers.</p> <p>21 Q. You identified, based on</p> <p>22 your opinion, no difference in the</p> <p>23 inflammation caused by talc and the</p> <p>24 inflammation caused by cadmium, correct?</p>

<p style="text-align: right;">Page 310</p> <p>1 A. I did not do talc inhalation 2 in my laboratory. The studies 3 indicate -- looked for the same thing. 4 They look for changes in gene expression 5 of activating transcription factors. 6 They did in the Shukla study. 7 They look for the percentage 8 of neutrophils. They look for macrophage 9 activation. We all look at the same 10 thing when coming to the conclusion of 11 inflammation. 12 Q. And according to you, talc 13 and cadmium act similarly with regard to 14 inducing inflammation in the lungs? 15 MS. O'DELL: Objection to 16 form. 17 THE WITNESS: Do they act 18 similarly? Well, I think I 19 answered that question. 20 Inflammation is -- is the -- 21 inflammation is modified by the 22 same components, the same soluble 23 factors, the same cell type 24 factors, including macrophages and</p>	<p style="text-align: right;">Page 312</p> <p>1 because I haven't investigated 2 that literature. 3 But inflammation -- 4 inflammation doesn't change. It 5 can get out of the particular 6 local organ. I don't think that 7 cadmium has been investigated in 8 terms of the ovary. It's 9 certainly been investigated in 10 terms of the kidney, which is 11 local -- which is systemically a 12 distant organ from the local 13 target, which is the lung. And it 14 can cause inflammation in the 15 kidney. 16 BY MR. HEGARTY: 17 Q. You haven't identified any 18 differences between the inflammation 19 caused by other particulates and the 20 inflammation caused by talc, correct? 21 MS. O'DELL: Objection to 22 form. 23 THE WITNESS: Inflammation 24 is inflammation.</p>
<p style="text-align: right;">Page 311</p> <p>1 neutrophils, dendritic cells, 2 whatever. So inflammation, 3 whether it's acute or chronic 4 inflammation used the same 5 parameters. 6 We call inflammation -- we 7 call inflammation when you -- in a 8 tissue or in organs when you see 9 these characteristics. And we say 10 these are markers indicative. 11 These are pathologies 12 indicative -- these are -- of an 13 inflammatory response. 14 BY MR. HEGARTY: 15 Q. So according to your 16 opinion, that's biologic plausibility 17 between cadmium exposure and ovarian 18 cancer? 19 MS. O'DELL: Objection to 20 form. 21 THE WITNESS: I would have 22 to do more research on that to be 23 able to say that. I would not say 24 biological plausibility, only</p>	<p style="text-align: right;">Page 313</p> <p>1 BY MR. HEGARTY: 2 Q. You referred to fragrances. 3 A. I'm sorry. Could you give 4 me a page? 5 Q. Over on Page 12. You cite 6 to a single study that discusses what 7 exposure levels of these fragrances have 8 been shown to induce a biologically 9 plausible effect in the ovary. 10 MS. O'DELL: Object to the 11 form. 12 THE WITNESS: Many of these 13 fragrances, many of these 14 chemicals within a specific 15 fragrance, it can consist of maybe 16 150 or even more chemicals within 17 any one given fragrance. Many of 18 them have been shown to cause 19 inflammation. 20 BY MR. HEGARTY: 21 Q. Have any of the chemicals in 22 the fragrances that you looked at been 23 reported in the medical literature to 24 induce inflammation in the ovaries?</p>

<p style="text-align: right;">Page 314</p> <p>1 A. No one specifically -- to my 2 knowledge, no one specifically looked at 3 inflammation in the ovaries. But again, 4 if you go back to the idea of 5 inflammation being caused by a particle 6 at a local site and then having the 7 potential -- or having the capacity I 8 should say, to -- to have that 9 inflammation go to a distant -- a more 10 distant site.</p> <p>11 So the fact that no one has 12 looked at it does not delete the fact 13 that certainly inflammation can get to 14 distant sites, including the ovary.</p> <p>15 Q. Well, what is the dose of 16 nickel or -- and cobalt and chromium 17 individually that must -- that the woman 18 must be exposed to in vivo to induce 19 inflammation in the ovaries?</p> <p>20 MS. O'DELL: Object to the 21 form. Asked and answered.</p> <p>22 THE WITNESS: There are -- 23 as I said, there's really -- one 24 particle, one piece can start the</p>	<p style="text-align: right;">Page 316</p> <p>1 metals, but there's also -- if you look 2 at nickel and it's a micronutrient, so 3 you can have very, very, very tiny 4 amounts in the body -- very tiny. And it 5 can be used as a micronutrient.</p> <p>6 You can have lead, but that 7 should not be in the body at all. And 8 there is no safe level of lead. So 9 despite what the regulatory agencies say, 10 there is no safe level which is what 11 their conclusion is moving towards.</p> <p>12 And -- so a metal is not a 13 metal is not a metal.</p> <p>14 Now, when you look at these 15 three metals, so for example you have 16 nickel which is classified as a 1A 17 carcinogen, but --</p> <p>18 Q. I'll withdraw the question. 19 You're not -- Doctor, you're not 20 answering my question.</p> <p>21 MS. O'DELL: She is 22 answering your question.</p> <p>23 MR. HEGARTY: No, she is 24 not.</p>
<p style="text-align: right;">Page 315</p> <p>1 process for inflammation. 2 BY MR. HEGARTY: 3 Q. So it -- 4 A. It could be one. 5 Q. -- it's your opinion that 6 one particle of nickel will induce 7 inflammation in the ovaries?</p> <p>8 MS. O'DELL: Objection.</p> <p>9 BY MR. HEGARTY: 10 Q. Is that correct? 11 A. Will? I can't -- I haven't 12 gone through the literature, but could, 13 certainly.</p> <p>14 Q. And what literature can you 15 cite that would say that one particle of 16 nickel could cause inflammation in the 17 ovary?</p> <p>18 A. It's my professional 19 judgment being an expert toxicologist in 20 the area of metals.</p> <p>21 Q. Okay. Same question as to 22 cobalt and chromium.</p> <p>23 A. Well, metals can't be lumped 24 together like that. Metals are indeed</p>	<p style="text-align: right;">Page 317</p> <p>1 MS. O'DELL: Yes, she is. 2 And if you don't -- let her 3 finish.</p> <p>4 MR. HEGARTY: Okay. 5 We'll -- we'll call Judge Pisano 6 and he'll see if we're asking the 7 question -- if she's answering the 8 question.</p> <p>9 MS. O'DELL: Are you 10 threatening the witness by saying 11 that?</p> <p>12 MR. HEGARTY: No, I'm 13 talking to you. We'll go off the 14 record --</p> <p>15 MS. O'DELL: You're 16 threatening the witness and -- no, 17 we're not going off the record.</p> <p>18 MR. HEGARTY: Go off the 19 record, let's go off the record.</p> <p>20 MS. O'DELL: No, we are not 21 going off the record.</p> <p>22 MR. HEGARTY: Yes, let's go 23 off the record.</p> <p>24 MS. O'DELL: If she's</p>

<p style="text-align: right;">Page 318</p> <p>1 answering your question, she --</p> <p>2 she gets the right to finish her</p> <p>3 answer. You don't cut her off,</p> <p>4 Mark.</p> <p>5 MR. HEGARTY: Let's go off</p> <p>6 the record.</p> <p>7 MS. O'DELL: No, we're not</p> <p>8 going off the record. She's</p> <p>9 finishing her answer.</p> <p>10 MR. HEGARTY: Let's go off</p> <p>11 the record. I'm not --</p> <p>12 MS. O'DELL: And then you</p> <p>13 can ask her another question.</p> <p>14 MR. HEGARTY: Let's go off</p> <p>15 the record. It's my deposition.</p> <p>16 MS. O'DELL: No. It's your</p> <p>17 deposition, but it's not fair to</p> <p>18 mistreat this witness if she is</p> <p>19 answering your question.</p> <p>20 MR. HEGARTY: I'm not</p> <p>21 mistreating the witness.</p> <p>22 MS. O'DELL: Yes, you are.</p> <p>23 MR. HEGARTY: We'll go off</p> <p>24 the record and call Judge Pisano.</p>	<p style="text-align: right;">Page 320</p> <p>1 either inhaled or applied to the perineum</p> <p>2 will induce inflammation in the ovaries?</p> <p>3 A. It's my opinion that it</p> <p>4 could.</p> <p>5 Q. What literature do you have</p> <p>6 to support that opinion?</p> <p>7 A. My professional opinion as a</p> <p>8 toxicologist in metals with over</p> <p>9 30 years.</p> <p>10 Q. Next question. Is it your</p> <p>11 opinion that one particle of cobalt,</p> <p>12 either inhaled or applied to the</p> <p>13 perineum, will induce inflammation in the</p> <p>14 ovaries?</p> <p>15 A. Again, it's my opinion that</p> <p>16 it -- it could. It has the biological</p> <p>17 plausibility to, because inflammation,</p> <p>18 although not as toxic in many ways as</p> <p>19 it's classified as a 2B -- 2B by IARC</p> <p>20 is -- has the potential -- does cause</p> <p>21 inflammation, and that inflammation can</p> <p>22 leave the site of the target site.</p> <p>23 Q. What authority do you have</p> <p>24 for that opinion?</p>
<p style="text-align: right;">Page 319</p> <p>1 MS. O'DELL: You are</p> <p>2 mistreating the witness by not</p> <p>3 allowing her to finish her --</p> <p>4 MR. HEGARTY: I withdrew the</p> <p>5 question.</p> <p>6 MS. O'DELL: Well, okay.</p> <p>7 The with -- the question was</p> <p>8 withdrawn. Ask a question, let</p> <p>9 her --</p> <p>10 MR. HEGARTY: No, we're off</p> <p>11 the record. We're going to call</p> <p>12 Judge Pisano.</p> <p>13 MS. O'DELL: Okay. Great.</p> <p>14 THE VIDEOGRAPHER: Off the</p> <p>15 record. The time is 3:21 p.m.</p> <p>16 Off the record.</p> <p>17 (Whereupon, a discussion was</p> <p>18 held off the record.)</p> <p>19 THE VIDEOGRAPHER: We are</p> <p>20 back on the record. The time is</p> <p>21 3:23 p.m.</p> <p>22 BY MR. HEGARTY:</p> <p>23 Q. Dr. Zelikoff, is it your</p> <p>24 opinion that one particle of nickel</p>	<p style="text-align: right;">Page 321</p> <p>1 A. My professional opinion.</p> <p>2 Q. Is it your opinion that one</p> <p>3 particle of chromium, either inhaled or</p> <p>4 applied to the perineum, will induce</p> <p>5 inflammation in the ovaries?</p> <p>6 MS. O'DELL: Objection to</p> <p>7 the form.</p> <p>8 THE WITNESS: It depends on</p> <p>9 the form of the chromium.</p> <p>10 BY MR. HEGARTY:</p> <p>11 Q. What form of chromium does</p> <p>12 it need to be?</p> <p>13 A. A trivalent chromium</p> <p>14 which -- I'm sorry, hexavalent chromium</p> <p>15 which will then get into the cell, start</p> <p>16 the process and -- and convert to</p> <p>17 chromium-3, 4 and 5.</p> <p>18 Q. That's chromium-6, correct?</p> <p>19 A. Hexavalent chromium is</p> <p>20 chromium-6, right.</p> <p>21 Q. Is it your opinion that one</p> <p>22 particle of chromium-6, either inhaled or</p> <p>23 applied to the perineum, will induce</p> <p>24 inflammation in the ovaries?</p>

<p style="text-align: right;">Page 322</p> <p>1 MS. O'DELL: Objection to</p> <p>2 form.</p> <p>3 THE WITNESS: It could,</p> <p>4 because inflammation again could</p> <p>5 leave the target site. And it</p> <p>6 depends on the form of the metal.</p> <p>7 So we have soluble metals --</p> <p>8 I don't want to go on too long.</p> <p>9 You have soluble metals and</p> <p>10 insoluble metals. Some of them</p> <p>11 are more toxic and more -- and</p> <p>12 potentially more carcinogenic than</p> <p>13 other forms. There are many salts</p> <p>14 within those metals that you gave.</p> <p>15 BY MR. HEGARTY:</p> <p>16 Q. And what authority do you</p> <p>17 have for the statement that one particle</p> <p>18 of chromium, either inhaled or applied to</p> <p>19 the perineum, will induce inflammation in</p> <p>20 the ovaries?</p> <p>21 A. My professional judgment.</p> <p>22 Q. Will one particle of the</p> <p>23 fragrance of the chemicals that you list</p> <p>24 from the fragrances, either inhaled or</p>	<p style="text-align: right;">Page 324</p> <p>1 lumped. And particles oftentimes,</p> <p>2 if they're different in size, if</p> <p>3 they're different in chemical</p> <p>4 structure, if they have iron or</p> <p>5 don't have iron, you have -- you</p> <p>6 may have differences.</p> <p>7 BY MR. HEGARTY:</p> <p>8 Q. Will one particle from</p> <p>9 diesel exhaust, inhaled or applied to the</p> <p>10 perineum, cause inflammation in the</p> <p>11 ovary?</p> <p>12 MS. O'DELL: Object to the</p> <p>13 form.</p> <p>14 THE WITNESS: Again, same</p> <p>15 answer, it could. Depends on the</p> <p>16 particle size, the particle type,</p> <p>17 the particle morphology. And it</p> <p>18 has the potential to induce</p> <p>19 inflammation as shown in cells.</p> <p>20 And can produce an oxidant state.</p> <p>21 BY MR. HEGARTY:</p> <p>22 Q. Doesn't inflammation just</p> <p>23 reflect the body's normal response to the</p> <p>24 presence of the particles?</p>
<p style="text-align: right;">Page 323</p> <p>1 applied to the perineum, cause</p> <p>2 inflammation to the ovaries?</p> <p>3 MS. O'DELL: Objection to</p> <p>4 the form.</p> <p>5 THE WITNESS: If -- I -- I</p> <p>6 don't have the knowledge, I don't</p> <p>7 have the literature knowledge to</p> <p>8 answer that question.</p> <p>9 BY MR. HEGARTY:</p> <p>10 Q. Will one -- will one</p> <p>11 particle of -- of cadmium, either inhaled</p> <p>12 or applied to the perineum, cause</p> <p>13 inflammation in the ovaries?</p> <p>14 A. It can cause --</p> <p>15 MS. O'DELL: Objection to</p> <p>16 form. You can answer.</p> <p>17 THE WITNESS: It can cause</p> <p>18 inflammation in the area if it's</p> <p>19 inhaled in the lung and that</p> <p>20 inflammation can get out</p> <p>21 systemically.</p> <p>22 Now it depends, again, on</p> <p>23 the size of the particle. Metals,</p> <p>24 as I said before, cannot be</p>	<p style="text-align: right;">Page 325</p> <p>1 A. There are two -- there are</p> <p>2 two forms of -- well, there are multiple</p> <p>3 forms of inflammation. But the two that</p> <p>4 are of concern and in -- in response to</p> <p>5 your question, is that they are acute</p> <p>6 inflammation and there is chronic</p> <p>7 inflammation.</p> <p>8 And with acute inflammation,</p> <p>9 the first response to a foreign -- a</p> <p>10 foreign particle or an antigen on a</p> <p>11 bacterial cell or an infectious agent, is</p> <p>12 for the body to mount an immune response.</p> <p>13 How it does that is through</p> <p>14 the same cell types that I just</p> <p>15 mentioned. Polymorphonucleocytes, also</p> <p>16 known as neutrophil. Macrophages, and</p> <p>17 those are the two key players, but</p> <p>18 natural killer cells all come into it.</p> <p>19 That involves the innate</p> <p>20 immune system. And so the first thing to</p> <p>21 protect the body, whether it's a viral</p> <p>22 infection or whether it's a bacterial</p> <p>23 infection or whether it's a foreign</p> <p>24 particle, is to mount that kind of immune</p>

<p style="text-align: right;">Page 326</p> <p>1 response to kill or negatively impact 2 that particular particle. 3 That will then -- that's an 4 innate immune response being active. 5 That will then, in some cases, upregulate 6 the T-cell and -- and humoral or -- and 7 cell-mediated immune response. 8 Now, that is, in terms of 9 cancers and in terms of tumors, that is 10 called immunosurveillance and that's the 11 first thing. And you're absolutely 12 right. The purpose of the immune system 13 is to protect the body. That is the 14 function. 15 However, there are three 16 stages or three types of processes for 17 the immune system in carcinogenesis. The 18 second being immuno equilibrium. But the 19 part that is the last part is that the 20 tumor can actually quiet or cause 21 immunosenescence of the immune system. 22 So in a chronic 23 inflammation, it does not always act in 24 the best interest of the -- of the host</p>	<p style="text-align: right;">Page 328</p> <p>1 inflammation. Not that they involve 2 different cell types or different 3 mechanisms. But they are called, in 4 terms of timing or temporality, acute 5 which will kill whatever right away and 6 then chronic which unfortunately keeps 7 playing back on itself and the 8 inflammation will continue. 9 Q. Granulomas which you just 10 mentioned don't cause cancer, correct? 11 A. Granulomas do not -- I'm 12 sorry. 13 Q. Granulomas which you just 14 mentioned don't cause cancer, correct? 15 A. Granulomas are in response 16 to a foreign body. In the case of 17 asbestos or in the case of another type 18 of fiber, macrophage will come over and 19 their normal process in what we call 20 innate immunity is to engulf the fiber. 21 And unfortunately, many times the fiber 22 cannot be engulfable or the particle 23 cannot be engulfable. 24 And so many macrophage will</p>
<p style="text-align: right;">Page 327</p> <p>1 but in the best interest of the tumor. 2 So your -- the answer to 3 your question is yes, that's the function 4 of it. But it can behave, it's a 5 two-prong sword. 6 Q. You said there are multiple 7 types of inflammation and you listed two 8 types: Acute and chronic. Are there any 9 other types besides those two? 10 A. Well, you have the reactions 11 to those inflammation in terms of having 12 a foreign body reaction. That is part of 13 an inflammatory response. So in terms of 14 temporality or timing, inflammation is 15 acute and is chronic. 16 What occurs during that 17 time, such as a foreign body reaction 18 where macrophages all come together and 19 engulf the particle or the fiber and try 20 to keep it within a localized space, that 21 is a process that can occur within 22 inflammation. 23 So my answer to you is that 24 there are two major types of</p>	<p style="text-align: right;">Page 329</p> <p>1 come over, and they will try to engulf it 2 as a body. And that is called a 3 granulomatous reaction. 4 And that's what happens 5 during tuberculosis when the organism 6 forms, many macrophages come over to kill 7 the organism, but it can't, and so they 8 form granulomas. 9 Q. Doctor, listen to my 10 question. I didn't ask you what a 11 granuloma was. I asked you, granulomas 12 don't cause cancer, correct? 13 MS. O'DELL: Object to form. 14 THE WITNESS: There is no 15 literature to my knowledge that 16 shows a granuloma, meaning immune 17 response, forming macrophages 18 engulfing, can cause cancer. 19 BY MR. HEGARTY: 20 Q. And a reaction to 21 inflammation can include the development 22 of fibrosis or scar tissue, correct? 23 A. That is a long-term chronic 24 response associated with chronic</p>

<p style="text-align: right;">Page 330</p> <p>1 inflammation.</p> <p>2 Q. And there's no literature</p> <p>3 linking fibrosis to cancer, correct?</p> <p>4 MS. O'DELL: Object to the</p> <p>5 form.</p> <p>6 THE WITNESS: My</p> <p>7 professional opinion is that there</p> <p>8 is literature -- let me just read</p> <p>9 over the question, please.</p> <p>10 So fibrosis is produced by</p> <p>11 release of factors from the</p> <p>12 macrophage. And it causes</p> <p>13 scarring within that particular</p> <p>14 target organ.</p> <p>15 Now, whether or not that --</p> <p>16 those -- that scarring can</p> <p>17 actually make that site more</p> <p>18 vulnerable to cancer, like in the</p> <p>19 case of hepatitis, where you get</p> <p>20 scarring, and you get cancer as a</p> <p>21 result of that particular</p> <p>22 fibrosis, but they are two</p> <p>23 different diseases.</p> <p>24 But whether the area of</p>	<p style="text-align: right;">Page 332</p> <p>1 A. Fibrosis does not morph or</p> <p>2 turn into cancer. That is correct.</p> <p>3 Q. In Section 12 -- I'm sorry.</p> <p>4 On Page 12, under your section</p> <p>5 "exposure," talc particle access to the</p> <p>6 body.</p> <p>7 Do you see that section?</p> <p>8 A. Is this Paragraph 1, 2, or</p> <p>9 3?</p> <p>10 Q. Well, I'm looking just at</p> <p>11 the Section Number 4 right now.</p> <p>12 A. Yes. Okay. Section Number</p> <p>13 6 is on Page 12.</p> <p>14 Q. Section 6. I'm sorry. I</p> <p>15 had those transposed.</p> <p>16 A. And please repeat your</p> <p>17 question.</p> <p>18 Q. You never -- prior to being</p> <p>19 contacted by counsel for plaintiffs, you</p> <p>20 never looked at the studies reporting on</p> <p>21 whether talc can reach the ovaries via</p> <p>22 inhalation or perineal application,</p> <p>23 correct?</p> <p>24 A. I did not study the</p>
<p style="text-align: right;">Page 331</p> <p>1 fibrosis creates a more vulnerable</p> <p>2 tissue base that can -- that can</p> <p>3 progress or go to cancer is a</p> <p>4 question that there is some</p> <p>5 examples of, but -- in the liver</p> <p>6 in particular.</p> <p>7 BY MR. HEGARTY:</p> <p>8 Q. Well, there's no literature</p> <p>9 reporting an increased risk of cancer in</p> <p>10 any organ because there's fibrosis in</p> <p>11 that organ, correct?</p> <p>12 A. What I'm saying is that in</p> <p>13 terms of the liver and in terms of</p> <p>14 fibrosis, let's say from ethanol or</p> <p>15 acetaminophen ingestion, you get fibrosis</p> <p>16 which is a whole disease or symptomology</p> <p>17 by itself, and then you have cancer,</p> <p>18 which is another disease. But what I'm</p> <p>19 saying is that in the area where the</p> <p>20 injury and the fibrosis occurs, in the</p> <p>21 liver there is a higher risk of getting</p> <p>22 cancer.</p> <p>23 Q. Fibrosis doesn't morph or</p> <p>24 turn into cancer?</p>	<p style="text-align: right;">Page 333</p> <p>1 literature or review the literature prior</p> <p>2 to being contacted. But I studied it and</p> <p>3 reviewed it extensively after being</p> <p>4 contacted.</p> <p>5 Q. On Page 12 of the last</p> <p>6 paragraph -- I'm sorry -- second-to-last</p> <p>7 paragraph, which begins, "A common</p> <p>8 exposure route."</p> <p>9 Do you see that paragraph?</p> <p>10 A. I do. Thank you.</p> <p>11 Q. You write, "Again, a common</p> <p>12 exposure route for cosmetic talc is via</p> <p>13 the dermal route including vaginally</p> <p>14 after perineal application."</p> <p>15 A. Yes.</p> <p>16 Q. Is it your testimony that</p> <p>17 there's biologic plausibility with talc</p> <p>18 applied to the skin?</p> <p>19 A. Applied to the skin, talc</p> <p>20 does not -- is not absorbed into the skin</p> <p>21 or through the skin, although there is</p> <p>22 some question as to whether if there's</p> <p>23 injury or scratch or openings in the</p> <p>24 skin, whether the talc can penetrate.</p>

<p style="text-align: right;">Page 334</p> <p>1 But in and of itself talc cannot 2 penetrate through the skin. 3 However, we're not -- when 4 we're talking about perineal or vaginal 5 application, you are not talking about an 6 epidermal subcutaneous keratinized skin. 7 Q. None of the studies that you 8 cite in this paragraph researched 9 particle transport through the 10 reproductive tract through perineal 11 application, correct? 12 MS. O'DELL: Object to the 13 form. 14 THE WITNESS: These -- it is 15 extremely technically difficult, 16 from my knowledge as an animal 17 toxicologist, to do perineal 18 application to a mouse. 19 BY MR. HEGARTY: 20 Q. I'm going to withdraw the 21 question. Doctor, you will not respond 22 to my question. My question is simply, 23 none of the studies that you cite in this 24 paragraph researched particle transport</p>	<p style="text-align: right;">Page 336</p> <p>1 the form. 2 BY MR. HEGARTY: 3 Q. Correct? 4 MS. O'DELL: Excuse me. You 5 may answer his question any way 6 you'd want to, Doctor. 7 THE WITNESS: None of these 8 that I have stated on Page 12 9 refer to perineal exposure in the 10 second paragraph in terms of 11 Venter, Iturralde, Sjosten and 12 Heller. 13 However, on Page -- on Page 14 13, there is a study by Keskin, 15 who used rats and did a vaginal or 16 perineum to talc. 17 BY MR. HEGARTY: 18 Q. I'm going to move to strike. 19 We're going to go off the record. 20 MR. HEGARTY: We're going to 21 call Judge Pisano. There's no 22 reason to add that additional part 23 to the answer to that question. 24 And I'm not -- I'm tired of that</p>
<p style="text-align: right;">Page 335</p> <p>1 through the reproductive tract through 2 perineal application. That's correct? 3 A. There is a study, and I'm 4 afraid the name of the author does not 5 come to me. So allow me to look at my 6 report. 7 Q. And I'm just talking about 8 the authorities that you cite in the 9 second paragraph beginning, "A common 10 exposure route." 11 MS. O'DELL: Feel free to 12 look at your report if you need 13 to, Doctor. 14 THE WITNESS: I understand. 15 On Page 13, animal models -- 16 BY MR. HEGARTY: 17 Q. Doctor, that's not my 18 question. My question is in the 19 paragraph that I referenced beginning a 20 common exposure route, none of those 21 authorities looked at transport of the 22 particles via application of those 23 particles to the perineum? 24 MS. O'DELL: Objection to</p>	<p style="text-align: right;">Page 337</p> <p>1 happening. So we'll call him 2 unless you're going to talk to the 3 witness. 4 MS. O'DELL: Is your 5 objection she didn't answer your 6 question? Because she -- you 7 asked her about the paragraph. 8 She said "no; however" -- 9 MR. HEGARTY: We're off the 10 record. 11 MS. O'DELL: No, we're not 12 off the record. 13 MR. HEGARTY: We're off the 14 record. 15 MS. O'DELL: No, we -- 16 MR. HEGARTY: We're going 17 off the record. 18 MR. LOCKE: We are off. Let 19 me throw out something. We've got 20 seven hours. I think there's a 21 plan here to stall, and we need to 22 do a better job of keeping things 23 moving, or we are going to have to 24 ask the court for more time.</p>

<p style="text-align: right;">Page 338</p> <p>1 MR. HEGARTY: Let's go off 2 the record. 3 MS. O'DELL: The suggestion 4 that there's -- let me just -- 5 before we go off the record, the 6 suggestion that there's somehow a 7 plan to -- is incorrect, and 8 improper. So if you want to go 9 off the record, I think you've got 10 an answer to your question, which 11 was, "No, not in the paragraph." 12 However, she has a right to 13 point to evidence in her report. 14 That's perfectly appropriate. 15 MR. HEGARTY: We'll let 16 Judge Pisano decide. We'll go off 17 the record. 18 THE VIDEOGRAPHER: The time 19 is 3:39 p.m. Going off the 20 record. 21 (Short break.) 22 THE VIDEOGRAPHER: The time 23 is 4:04 p.m. Back on the record. 24 MR. HEGARTY: We're back on</p>	<p style="text-align: right;">Page 340</p> <p>1 have looked at transport of dry powder 2 talc to the perineum showing that the -- 3 that talc transports to the ovaries, 4 correct? 5 MS. O'DELL: Object to the 6 form. 7 THE WITNESS: When we say -- 8 when you say talc, you're 9 referring to talcum powder 10 products? 11 BY MR. HEGARTY: 12 Q. Correct, correct. 13 A. That's correct to my 14 knowledge. 15 Q. And are you aware that talc 16 is in toilet paper? 17 A. Yes, I just learned that 18 recently. 19 Q. Can talc in toilet paper 20 migrate to the ovaries? 21 MS. O'DELL: Object to the 22 form. 23 THE WITNESS: Can -- my 24 knowledge is that talc in toilet</p>
<p style="text-align: right;">Page 339</p> <p>1 the record and we're going to 2 continue without calling Judge 3 Pisano at this time. But we do 4 reserve the right to ask Judge 5 Pisano for more time based on our 6 belief that Dr. Zelickoff has many 7 occasions over the course of this 8 deposition not been responsive to 9 the questions asked and as a 10 result has -- has wasted the 11 defendant's time and to our 12 prejudice. 13 So -- but we're going to go 14 forward and see if we can finish 15 this deposition. 16 MS. O'DELL: Plaintiffs will 17 obviously oppose that -- that 18 motion. Dr. Zelickoff has been 19 responsive to your questions. 20 BY MR. HEGARTY: 21 Q. Dr. Zelickoff, we're talking 22 about the section on talc particle's 23 access to the body. There have been no 24 studies in either animals or humans that</p>	<p style="text-align: right;">Page 341</p> <p>1 paper is -- is bound to the 2 other -- the other components 3 there. So unless it becomes 4 bioavailable it cannot migrate 5 from the toilet paper. 6 BY MR. HEGARTY: 7 Q. How about talc -- talc in 8 soap, is there talc in soaps? 9 A. To my knowledge there is. 10 Q. Can talc in soaps, if 11 applied to the perineum, migrate to the 12 ovaries? 13 A. If it becomes -- 14 MS. O'DELL: Object to form. 15 THE WITNESS: If it becomes 16 bioavailable. Likely bound up to 17 the other components. 18 BY MR. HEGARTY: 19 Q. When you say bioavailable, 20 what do you mean? 21 A. To me, "bioavailable" means 22 that the body can see it, and it 23 becomes -- it becomes -- it has access to 24 biological responsiveness.</p>

<p style="text-align: right;">Page 342</p> <p>1 Q. And do you know a 2 Dr. Benjamin Neel at NY University -- New 3 York University? 4 A. Dr. Neel, isn't he the head 5 of the cancer center? 6 Q. He is. 7 A. He is the head of the cancer 8 center. 9 Q. Do you know him? 10 A. I do not know him. 11 Q. Does he know more about 12 cancer biology than you do? 13 MS. O'DELL: Object to the 14 form. 15 THE WITNESS: I've not seen 16 his CV. I would assume as head of 17 the cancer center, that he 18 probably does. Since that is not 19 my area of study. 20 BY MR. HEGARTY: 21 Q. Are dose-response 22 relationships important in evaluating 23 potential carcinogenicity of a substance? 24 A. Dose-response --</p>	<p style="text-align: right;">Page 344</p> <p>1 Q. You need a specific page? 2 Over on Page 16. Over the course of this 3 page and carrying over to the next page, 4 you cite a number of studies that refer 5 to talc causing pleural inflammation, 6 correct? 7 A. Yes. 8 Q. Talc causing granulomas, 9 correct? 10 A. Yes. 11 Q. Talc causing pulmonary 12 interstitial fibrosis, correct? 13 A. Talcum powder can do those 14 things, yes. 15 Q. And talc causing 16 carcinogenic activity in the lungs, 17 correct? 18 A. Are you referring to a 19 specific line? 20 Q. No, I'm not referring to a 21 specific line. I'm talking about 22 generally from this part of your report. 23 A. In general, this is the 24 section on inhalation. I'm talking</p>
<p style="text-align: right;">Page 343</p> <p>1 dose-responses are -- contribute to, as I 2 said frequency, duration, exposure route. 3 They all contribute to carcinogenicity. 4 Q. In other words, in 5 evaluating the carcinogenicity of a 6 substance, it's important to look at dose 7 relationships, correct? 8 A. Are you speaking about 9 dose-response, or more than one dose? 10 Q. Let me ask it again. In 11 evaluating the substance for 12 carcinogenicity purposes, it's important 13 to look at dose-response relationships, 14 correct? 15 A. It's important to look at 16 dose-response relationships, but it's not 17 the only factor, is what I'm saying. 18 Q. In your report, you cite a 19 number of reactions to talc that have 20 been reported, pleural inflammation, 21 granulomas, pulmonary 22 interstitial fibrosis -- 23 A. What page are you referring 24 to?</p>	<p style="text-align: right;">Page 345</p> <p>1 about -- yes, I'm talking about talcum 2 powder and its ability to bring about 3 changes in the lungs that could lead to 4 carcinogenic -- carcinogenesis. 5 Q. Of the reactions that we 6 just talked about, have any of those been 7 reported in women using talc on the 8 perineum? 9 A. There have been no studies 10 to my knowledge showing that application 11 of perineal talc can produce -- produces 12 lesions in the lungs. 13 Q. And there's been no studies 14 that you are -- of which you are aware 15 that have reported findings of granulomas 16 in women using talc in the perineum, 17 correct? 18 A. There is evidence of 19 inflammation clearly, but there -- to my 20 knowledge, I have not seen any of the 21 literature which shows a granuloma in the 22 ovary. 23 Q. What studies have you seen 24 that have reported seeing inflammation in</p>

<p style="text-align: right;">Page 346</p> <p>1 the ovaries of women using talc on the 2 perineum?</p> <p>3 MS. O'DELL: Object to the 4 form.</p> <p>5 THE WITNESS: I'm just 6 trying to find the section.</p> <p>7 There were many studies, I 8 can't right now, without finding 9 it in my report, identify any one 10 in particular.</p> <p>11 BY MR. HEGARTY:</p> <p>12 Q. Well, sitting here today, 13 can you cite any study that has reported 14 on finding inflammation of the ovaries 15 following perineal application of talc?</p> <p>16 A. As I said, there are many -- 17 there are many examples in animal models 18 that was not perineal, that was vaginal, 19 as you stated.</p> <p>20 There were studies -- 21 study -- an early study which identified 22 talcum powder particles in the ovary with 23 inflammatory responsiveness or 24 inflammatory responses. That was a</p>	<p style="text-align: right;">Page 348</p> <p>1 disease.</p> <p>2 Q. Okay. Rheumatoid arthritis 3 does not increase the risk of cancer, 4 correct?</p> <p>5 A. Rheumatoid arthritis, for 6 what's known now, does not increase the 7 risk of cancer.</p> <p>8 Q. Psoriasis is another chronic 9 inflammatory process, correct?</p> <p>10 A. Another autoimmune disease 11 and another inflammatory process, yes.</p> <p>12 Q. Having psoriasis does not 13 increase the risk of any form of cancer, 14 correct?</p> <p>15 A. Not that -- not that we know 16 with the current knowledge.</p> <p>17 Q. So just having chronic 18 inflammation does not mean cancer will 19 develop, correct?</p> <p>20 MS. O'DELL: Object to the 21 form.</p> <p>22 THE WITNESS: Just having 23 chronic inflammation does not have 24 to indicate. It's one -- again,</p>
<p style="text-align: right;">Page 347</p> <p>1 very -- that was a very early study. I'm 2 not sure if it was Hamilton or Henderson. 3 If I may.</p> <p>4 I'm sorry it's not coming to 5 mind now.</p> <p>6 Q. Okay. Over on Page 20 you 7 discuss the role of the immune system --</p> <p>8 A. Yes, sir.</p> <p>9 Q. -- correct?</p> <p>10 A. I see that, yes.</p> <p>11 Q. You agree that it's not 12 generally accepted by the medical or 13 scientific communities that all cancers 14 are caused by chronic inflammation, 15 correct?</p> <p>16 A. There are other mechanisms 17 that are associated with carcinogenesis 18 and the process of carcinogenesis. If 19 you'd like, I can identify those.</p> <p>20 Q. You agree that there are 21 types of chronic inflammation that are 22 not related to cancer. Rheumatoid 23 arthritis is one, correct?</p> <p>24 A. That's an autoimmune</p>	<p style="text-align: right;">Page 349</p> <p>1 it's one mechanism that provides 2 biological plausibility for the 3 cancer induction.</p> <p>4 If I may give an example.</p> <p>5 BY MR. HEGARTY:</p> <p>6 Q. Well, let me -- that's not 7 what I asked you for.</p> <p>8 A. Okay. I thought I answered 9 your question.</p> <p>10 Q. Does having pelvic 11 inflammatory disease cause ovarian 12 cancer?</p> <p>13 A. The inflammation has been 14 linked with ovarian cancer, yes.</p> <p>15 Q. In your opinion is there a 16 biologically plausible mechanism between 17 PID and ovarian cancer?</p> <p>18 A. Well, PID is usually 19 associated with an infection. And what's 20 related to cancer and why there's higher 21 risk in inflammatory diseases of 22 endometriosis and pelvic inflammatory 23 disease is through a mechanism of 24 inflammation.</p>

<p style="text-align: right;">Page 350</p> <p>1 Q. Your biologically plausible 2 mechanism for talc and ovarian cancer is 3 inflammation, correct? 4 A. That's primary, yes. 5 Q. You make reference to MUC-1. 6 That's not your biological plausibility 7 mechanism, is it? 8 A. You mean MUC-1 -- 9 Q. Yes. 10 A. -- antibodies? 11 Q. Correct? 12 A. MUC-1, if I may explain it, 13 is mucin. And -- 14 Q. I don't want to interrupt. 15 I'm not after an explanation. I just 16 wanted to know whether it's part -- 17 whether the references you include in 18 your report to MUC-1 are included in your 19 biologically plausible opinion? 20 A. It is included in my -- in 21 reaching my opinion, yes. 22 Q. Is that a separate mechanism 23 from inflammation? 24 A. It is a separate mechanism</p>	<p style="text-align: right;">Page 352</p> <p>1 A. It's -- the only evidence 2 out there that addresses this is when 3 they do correlation studies with the 4 level of antibodies to MUC-1. And when 5 the antibody levels are decreased, then 6 you have -- they found that you have an 7 increased risk of ovarian cancer. 8 Q. There are no studies 9 reporting or correlating MUC-1 levels in 10 talcum powder users to ovarian cancer 11 risk, correct? 12 MS. O'DELL: Object to form. 13 THE WITNESS: Not to my 14 knowledge. 15 MS. O'DELL: Sorry. 16 BY MR. HEGARTY: 17 Q. And measuring MUC-1 is not 18 used to diagnose ovarian cancer, correct? 19 A. MUC-1 is also known as 20 CA-125, and it is used as a marker. 21 Q. My question is, is MUC-1 22 used to -- levels -- strike that. 23 Are MUC-1 levels used to 24 diagnose a woman with ovarian cancer?</p>
<p style="text-align: right;">Page 351</p> <p>1 from inflammation. It's seen in ovarian 2 cancer as a marker. And when you have -- 3 evidence has shown that if you have 4 antibodies to MUC-1, and if they're 5 decreased as is seen in response to talc, 6 that you will have less of an immune 7 response and protection. 8 Q. Can you cite for me any 9 study that has correlated MUC-1 levels 10 with ovarian cancer risk? 11 MS. O'DELL: Object to form. 12 THE WITNESS: They use it as 13 a marker. The literature uses 14 MUC-1 as a marker of cancer. Can 15 I cite you any studies that links 16 it with ovarian cancer? No, I 17 cannot. 18 BY MR. HEGARTY: 19 Q. Are there any studies that 20 link the levels of MUC-1 to ovarian 21 cancer risk? 22 A. Do you mean human studies or 23 animal? 24 Q. Yes, human studies only.</p>	<p style="text-align: right;">Page 353</p> <p>1 A. My response to that is MUC-1 2 is synonymous with CA-125. CA-125 is a 3 shed marker in the blood associated with 4 ovarian cancer, so yes. 5 Q. Okay. Is it your testimony 6 that for purposes of -- strike that. 7 Is it your testimony that 8 CA-125 levels are used to diagnose 9 ovarian cancer? 10 MS. O'DELL: Object to the 11 form. 12 THE WITNESS: I'm saying 13 that CA-125 is used as a 14 biological marker of progression, 15 extent, and intensity and whether 16 ovarian cancer is present. 17 BY MR. HEGARTY: 18 Q. My question is, in a woman 19 who comes in complaining of symptoms that 20 might be ovarian cancer, is CA-125 used 21 to diagnose ovarian cancer? 22 A. I'm sorry, I'm not a 23 physician. I can't answer that question 24 in terms of what -- what an OB/GYN or an</p>

<p style="text-align: right;">Page 354</p> <p>1 oncologist would do.</p> <p>2 Q. And measuring CA-125 levels</p> <p>3 does not give you any evidence of the</p> <p>4 etiology of the ovarian cancer, correct?</p> <p>5 A. Not to the etiology.</p> <p>6 However, it is an epithelial-associated</p> <p>7 protein.</p> <p>8 So if we are talking about</p> <p>9 epithelial, and we are talking about</p> <p>10 epithelial ovary carcinoma, it is related</p> <p>11 to -- to that.</p> <p>12 Q. Does all types -- do all</p> <p>13 types of inflammation irreparably damage</p> <p>14 tissue?</p> <p>15 A. Irreparably. Do you mean</p> <p>16 persistently without -- is there</p> <p>17 recovery?</p> <p>18 Q. No, my question is do all</p> <p>19 types of inflammation, all acute, all</p> <p>20 chronic inflammation, damage tissue where</p> <p>21 it's not repaired?</p> <p>22 A. Where it's not repaired?</p> <p>23 Q. Yes.</p> <p>24 A. No, you can have -- with</p>	<p style="text-align: right;">Page 356</p> <p>1 the systematic review of the</p> <p>2 literature as I have. But each</p> <p>3 doctor, I'm sure, makes their own</p> <p>4 opinion.</p> <p>5 BY MR. HEGARTY:</p> <p>6 Q. Can you cite any doctor who</p> <p>7 treats ovarian cancer or researches</p> <p>8 ovarian cancer who believes that the</p> <p>9 biological plausible mechanism of ovarian</p> <p>10 cancer is inflammation?</p> <p>11 A. I have not spoken to any</p> <p>12 doctors in that regard.</p> <p>13 Q. What does the inflammation</p> <p>14 in the ovary look like in your opinion</p> <p>15 from talc exposure?</p> <p>16 A. It looks like any other</p> <p>17 local target of inflammation, in that</p> <p>18 there are neutrophils, immune cells that</p> <p>19 migrate into the area. There are</p> <p>20 macrophages that migrate into the area.</p> <p>21 There can be higher levels of cytokines</p> <p>22 like interleukin and chemotactic factor,</p> <p>23 growth factor.</p> <p>24 Q. Such inflammation, if it was</p>
<p style="text-align: right;">Page 355</p> <p>1 acute inflammation, of course you can</p> <p>2 have repair of -- it's there to protect</p> <p>3 against the invader.</p> <p>4 Q. Does having inflammation in</p> <p>5 one organ or one tissue in the body</p> <p>6 always mean that other tissues in the</p> <p>7 body will be inflamed?</p> <p>8 A. It does not always mean</p> <p>9 that.</p> <p>10 Q. The medical community has</p> <p>11 not generally accepted that chronic</p> <p>12 inflammation is a cause of ovarian</p> <p>13 cancer, correct?</p> <p>14 MS. O'DELL: Objection to</p> <p>15 form.</p> <p>16 THE WITNESS: Again, I'm not</p> <p>17 quite sure what you mean by</p> <p>18 generally accepted. Everyone</p> <p>19 has -- every medical community has</p> <p>20 its own opinion. I'm sure there</p> <p>21 are many doctors who do embrace</p> <p>22 it. And I'm sure there are many</p> <p>23 doctors who do not. I'm not sure</p> <p>24 whether they've done the extent of</p>	<p style="text-align: right;">Page 357</p> <p>1 occurring would be visible, correct?</p> <p>2 A. Not necessarily. In a -- in</p> <p>3 a chronic -- first of all, you can get</p> <p>4 different time periods. So</p> <p>5 inflammation -- if it's chronic</p> <p>6 inflammation you are talking about one</p> <p>7 thing. And then you might see some</p> <p>8 remnants of the inflammation.</p> <p>9 But if you look at a period</p> <p>10 of time, you can miss the inflammatory</p> <p>11 response. It can be there, impact the</p> <p>12 cells and then be gone.</p> <p>13 Q. Even with chronic</p> <p>14 inflammation?</p> <p>15 A. With chronic inflammation,</p> <p>16 if you looked hard enough you would find</p> <p>17 the remnants of its presence and you will</p> <p>18 also likely find neutrophilic</p> <p>19 infiltration.</p> <p>20 Q. Has that --</p> <p>21 A. That does not last forever.</p> <p>22 Q. Has that ever -- that --</p> <p>23 those findings ever been reported in</p> <p>24 women using talc in the perineum?</p>

<p style="text-align: right;">Page 358</p> <p>1 A. The inflammatory response?</p> <p>2 Q. Correct.</p> <p>3 A. Or the infiltration? Not</p> <p>4 that I'm aware of. Not in my report.</p> <p>5 Q. How many applications of</p> <p>6 talc to the perineum does it take to</p> <p>7 cause chronic inflammation in the</p> <p>8 ovaries?</p> <p>9 A. That's -- that</p> <p>10 information -- that is not known how many</p> <p>11 applications, whether it could be one or</p> <p>12 it needs to be over a period of three</p> <p>13 years or a period of ten years. Some of</p> <p>14 the meta-analysis evaluations indicated</p> <p>15 that there were some temporal</p> <p>16 associations with it, and that it needed</p> <p>17 to be used longer than ten years, where</p> <p>18 you saw responsiveness. And others</p> <p>19 indicated less than ten years.</p> <p>20 So it's -- it's difficult to</p> <p>21 say, and it's also associated with the</p> <p>22 woman.</p> <p>23 Q. Does acute inflammation</p> <p>24 cause cancer?</p>	<p style="text-align: right;">Page 360</p> <p>1 Q. None of those inflammatory</p> <p>2 markers are tested to diagnose or monitor</p> <p>3 a woman for developing ovarian cancer,</p> <p>4 correct?</p> <p>5 A. To my knowledge, tumor</p> <p>6 necrosis factors, C-reactive protein,</p> <p>7 none of the interleukins are monitored.</p> <p>8 But again, I have to say</p> <p>9 that I'm not an OB/GYN and so I'm not --</p> <p>10 I'm not familiar with what their -- what</p> <p>11 they are using other than what's in the</p> <p>12 literature.</p> <p>13 Q. And no study has clinically</p> <p>14 correlated those markers with ovarian</p> <p>15 cancer or ovarian cancer risk, correct?</p> <p>16 MS. O'DELL: Objection to</p> <p>17 form.</p> <p>18 THE WITNESS: In looking at</p> <p>19 biological plausibility, which</p> <p>20 I'm -- which I'm focused on, the</p> <p>21 indication of those elevated</p> <p>22 levels as well as decreased levels</p> <p>23 of antioxidants are associated</p> <p>24 with inflammation and are</p>
<p style="text-align: right;">Page 359</p> <p>1 A. Acute inflammation has not</p> <p>2 been linked to my knowledge to cancer.</p> <p>3 As I said, it's used as an immune</p> <p>4 surveillance and protective mechanism as</p> <p>5 you pointed out.</p> <p>6 Q. Over on Pages 20 and 21 of</p> <p>7 your report you refer to CRP and other</p> <p>8 inflammatory markers, cytokines,</p> <p>9 inflammatory mediators. Do you see the</p> <p>10 section I'm referring to?</p> <p>11 A. I -- roles of the immune</p> <p>12 system, and then Section E, ovarian</p> <p>13 cancer inflammation?</p> <p>14 Q. Correct.</p> <p>15 A. Which section are you</p> <p>16 referring to?</p> <p>17 Q. Well, the section ovarian</p> <p>18 cancer inflammation at the bottom of</p> <p>19 Page 20, carrying over to the top of</p> <p>20 Page 21.</p> <p>21 A. I see that.</p> <p>22 Q. And there you talk about a</p> <p>23 number of inflammatory markers, correct?</p> <p>24 A. Correct.</p>	<p style="text-align: right;">Page 361</p> <p>1 associated with ovarian cancer.</p> <p>2 BY MR. HEGARTY:</p> <p>3 Q. Well, can you cite for me</p> <p>4 any study that has clinically correlated</p> <p>5 those findings to ovarian cancer risk?</p> <p>6 MS. O'DELL: Objection.</p> <p>7 Asked and answered.</p> <p>8 THE WITNESS: First of all,</p> <p>9 I'm not -- and again, not an</p> <p>10 OB/GYN.</p> <p>11 I can tell you that those</p> <p>12 risk factors, which are</p> <p>13 inflammatory markers, are used as</p> <p>14 an indicator of inflammation as a</p> <p>15 biological plausible mechanism.</p> <p>16 BY MR. HEGARTY:</p> <p>17 Q. Well, do you cite in your</p> <p>18 paper any studies that have --</p> <p>19 A. I'm sorry, do you mean the</p> <p>20 report?</p> <p>21 Q. In your report. Do you cite</p> <p>22 in your report any studies that have</p> <p>23 found that women with these markers have</p> <p>24 a higher -- higher or an increased risk</p>

<p style="text-align: right;">Page 362</p> <p>1 of ovarian cancer?</p> <p>2 A. Well, what I -- no. But</p> <p>3 what I have found is that in women who</p> <p>4 have ovarian cancer, when they measure</p> <p>5 concurrently or subsequently, that the</p> <p>6 levels of certain inflammatory markers</p> <p>7 are elevated.</p> <p>8 Q. My question was specific to</p> <p>9 women prior to being diagnosed with</p> <p>10 ovarian cancer, has any study shown that</p> <p>11 women with higher levels of these</p> <p>12 inflammatory markers have an increased</p> <p>13 risk of ovarian cancer?</p> <p>14 MS. O'DELL: Objection to</p> <p>15 form.</p> <p>16 THE WITNESS: Not in that</p> <p>17 particular context. But again I'm</p> <p>18 not an OB/GYN.</p> <p>19 BY MR. HEGARTY:</p> <p>20 Q. Has any study shown that</p> <p>21 these inflammatory factors are elevated</p> <p>22 in women using talc on the perineum?</p> <p>23 MS. O'DELL: Objection to</p> <p>24 the form.</p>	<p style="text-align: right;">Page 364</p> <p>1 are a normal product of cell activity,</p> <p>2 correct?</p> <p>3 A. That is correct --</p> <p>4 Q. For example, for many --</p> <p>5 A. -- for many cells.</p> <p>6 Q. -- reactive oxygen species</p> <p>7 increase if we exercise, correct?</p> <p>8 A. As well as antioxidants</p> <p>9 increase, yes.</p> <p>10 Q. The same is true for</p> <p>11 reactive nitrogen species, correct?</p> <p>12 A. Yes.</p> <p>13 Q. These --</p> <p>14 A. It's a matter of degree.</p> <p>15 Q. Reactive oxygen species and</p> <p>16 reactive nitrogen species increase if</p> <p>17 we're under stress, correct?</p> <p>18 A. They have been shown to do</p> <p>19 that, yes.</p> <p>20 Q. And the body has defense</p> <p>21 mechanisms to handle this increase in</p> <p>22 reactive oxygen species and reactive</p> <p>23 nitrogen species, correct?</p> <p>24 MS. O'DELL: Objection to</p>
<p style="text-align: right;">Page 363</p> <p>1 THE WITNESS: It's not a</p> <p>2 common thing to measure</p> <p>3 inflammatory mediators as a result</p> <p>4 of the common use of talcum powder</p> <p>5 products. So there is no</p> <p>6 indication of that because there</p> <p>7 are no studies of that.</p> <p>8 BY MR. HEGARTY:</p> <p>9 Q. If you look over on Page 24</p> <p>10 of your report under the section Role of</p> <p>11 Oxidants in Ovarian Cancer. Do you see</p> <p>12 that section?</p> <p>13 A. Section C on Page 24?</p> <p>14 Q. Correct.</p> <p>15 A. Yes.</p> <p>16 Q. All the processes that you</p> <p>17 describe in this section occur in</p> <p>18 everyone everyday, correct?</p> <p>19 MS. O'DELL: Object to the</p> <p>20 form.</p> <p>21 THE WITNESS: To a degree,</p> <p>22 yes.</p> <p>23 BY MR. HEGARTY:</p> <p>24 Q. The reactive oxygen species</p>	<p style="text-align: right;">Page 365</p> <p>1 form.</p> <p>2 THE WITNESS: The body has</p> <p>3 antioxidant mechanisms, including</p> <p>4 superoxide dismutase, catalase, et</p> <p>5 cetera, that are -- that elevate</p> <p>6 in response to reactive oxygen</p> <p>7 species. But they can be</p> <p>8 overwhelmed by the amount of ROS</p> <p>9 release.</p> <p>10 BY MR. HEGARTY:</p> <p>11 Q. But it would be improper to</p> <p>12 say that simply by the generation of</p> <p>13 reactive oxygen species or reactive</p> <p>14 nitrogen species, DNA mutations and tumor</p> <p>15 development will occur, correct?</p> <p>16 MS. O'DELL: Object to form.</p> <p>17 THE WITNESS: One couldn't</p> <p>18 say that just by the -- as you</p> <p>19 point out, as the normal -- under</p> <p>20 normal circumstances, endogenously</p> <p>21 within the body, and not in</p> <p>22 response to a particular agent</p> <p>23 does produce these. So one cannot</p> <p>24 say, to answer your question, that</p>

<p style="text-align: right;">Page 366</p> <p>1 it -- just the presence of 2 reactive oxygen species will lead 3 to cancer. 4 BY MR. HEGARTY: 5 Q. What data shows that the 6 body's response system to reactive oxygen 7 species and reactive nitrogen species is 8 unable to handle those species that might 9 be generated by talc exposure? 10 A. Numerous cell studies and 11 numerous animal studies. And you would 12 look at that by the level of antioxidants 13 that are also present. And if a 14 substance such as talcum powder product 15 reduces antioxidants, then the cell or 16 the tissue is going to be overwhelmed by 17 that product. 18 Q. Has that process ever been 19 shown in vivo? 20 A. In a -- I'm not sure if this 21 answers your question. I'll do my best 22 to answer it. And your question was has 23 that process, meaning the process of 24 antioxidant change -- is that your</p>	<p style="text-align: right;">Page 368</p> <p>1 of the literature comes from in vivo 2 animal studies as well as in vitro cell 3 studies. But my role is to -- is to look 4 at biological plausibility. And so 5 studies that reveal or indicate that 6 response in an animal model and in cell 7 culture indicates to me that there's no 8 likely reason why it could not happen in 9 women. 10 Q. Okay. At the top of Page 25 11 of your report, you say that even a 12 single dose of a carcinogen can produce 13 effects that are adverse to cells and 14 tissue at the site of exposure. 15 Do you see where I'm 16 reading? 17 A. Yes. 18 Q. When you say dose, do you 19 mean exposure at a dose or volume of 20 exposure to a substance that studies have 21 proven are adverse to cells and tissues? 22 MS. O'DELL: Object to the 23 form. 24 THE WITNESS: That's a</p>
<p style="text-align: right;">Page 367</p> <p>1 question? 2 Q. No. The process where the 3 cell or the tissue is going to be 4 overwhelmed, has that process ever been 5 shown in vivo in women? 6 A. In women? 7 Q. Yes. 8 MS. O'DELL: Object to the 9 form. You can answer. 10 THE WITNESS: Certainly in 11 animals, but not to my knowledge 12 in women. 13 I'm sorry. I'm still 14 thinking. 15 Whenever the antioxidant 16 levels are decreased, that is an 17 indicator of being overwhelmed by 18 the reactive oxygen species or the 19 oxidation stress. 20 BY MR. HEGARTY: 21 Q. And what studies have shown 22 the antioxidant levels are decreased in 23 women using talc? 24 A. In women using talc -- most</p>	<p style="text-align: right;">Page 369</p> <p>1 multiple question. But when I 2 refer to even a single dose, I 3 mean even a single exposure. 4 BY MR. HEGARTY: 5 Q. Are you saying there a 6 single molecule of the substance? 7 A. What I meant in this report 8 is even a single exposure. The 9 concentration of which could be unknown. 10 A single exposure to a certain 11 concentration, whatever that 12 concentration is, can produce effects. 13 I'm not saying can produce cancer. What 14 I'm saying is can start the process of 15 either inflammation or oxidative stress. 16 Q. And to what tissue does that 17 single dose need to reach to have the 18 adverse effects that you describe there? 19 MS. O'DELL: Object to the 20 form. 21 THE WITNESS: Whatever that 22 particular -- it depends upon the 23 carcinogen or the inflammagogue 24 that one is looking at in terms of</p>

<p style="text-align: right;">Page 370</p> <p>1 a single exposure. And it depends 2 on the susceptibility of the 3 tissue. So to answer your 4 question, doses or concentration 5 to the target tissue is unknown or 6 open. 7 BY MR. HEGARTY: 8 Q. You're not saying that a 9 single application of talc to the 10 perineum can produce effects that are 11 adverse to cells and tissue in the 12 ovaries, correct? 13 MS. O'DELL: Object to the 14 form. 15 THE WITNESS: I'm not saying 16 that it can't. I think I 17 testified earlier that a single -- 18 depending upon what that product 19 is -- in this case we're talking 20 about talcum powder product -- 21 that one exposure, one 22 application, one perineal direct 23 exposure could in fact trigger the 24 cells to start a process leaning</p>	<p style="text-align: right;">Page 372</p> <p>1 A. In women? 2 Q. Yes. 3 A. I can -- I cannot off the 4 top of my head or looking at my report 5 tell you that. Again, I just want to 6 repeat that my charge was to look at 7 biological plausibility and I -- I see 8 those effects or processes that you're 9 indicating in cells and animal models, 10 but I do not have that information with 11 humans. 12 Q. Are you aware of any study 13 correlating the exposures used in those 14 cell and animal models to the exposures 15 that women would experience with perineal 16 application of talc? 17 MS. O'DELL: Object to the 18 form. 19 THE WITNESS: Well, in my 20 mind, and in reality, women use 21 different amounts, whether it's 22 different handfuls. So I can't 23 really give you a concentration. 24 But there are studies, the in</p>
<p style="text-align: right;">Page 371</p> <p>1 towards inflammation. 2 BY MR. HEGARTY: 3 Q. And where the talc -- where 4 does the talc need to go in the body to 5 trigger that mechanism? 6 A. Well, once it gets -- once 7 it's applied to the perineal region, it's 8 my belief that it then migrates up to 9 the -- to the vaginal area. And in the 10 vaginal area, it could also start 11 mechanisms, gene expression changes in 12 the vaginal tissues that could lead to 13 inflammation, or it could get to the 14 point of the cervix or to the fallopian 15 tubes. It causes changes in cells, 16 whether it's gene expression or an 17 inflammation, at any one of those 18 upward -- upward reproductive tract organ 19 systems or tissues. They're all made up 20 of cells that are susceptible to oxidant 21 stress. 22 Q. Can you cite to us any study 23 that has shown that process in women 24 using talc to the perineum?</p>	<p style="text-align: right;">Page 373</p> <p>1 vitro studies, that did use more. 2 However, when you're looking 3 at toxicology and you're looking 4 to define a mechanism or a 5 potential mechanism, if you use 6 even a higher dose, you're 7 still -- you still can elicit the 8 same mechanism. 9 So perineal application -- 10 to answer your question, perineal 11 application can put a lot or a 12 little. But it also depends on 13 the frequency and the duration of 14 the use. 15 BY MR. HEGARTY: 16 Q. Doctor, my question, though, 17 was, has any study correlated the 18 exposures in the animal or cell studies 19 to which you are referring to, to show 20 that those same exposures are occurring 21 in women applying talc to the perineum? 22 A. No. 23 Q. For purposes of your 24 opinions on biological plausibility, do</p>

<p style="text-align: right;">Page 374</p> <p>1 you rely on the studies that you cite in 2 your report done by Dr. Saed? 3 A. I relied on the information 4 from Dr. Saed. It went into making up my 5 opinion, yes. 6 Q. If those studies were not 7 available to you, would your opinions 8 still be the same? 9 A. As I said, one of the -- one 10 of the manuscripts came after my report. 11 And it was -- I looked at an abstract, so 12 I had information. And other -- others 13 of Dr. Saed's I reviewed. But I would 14 have come to the same conclusion. That 15 was just -- that was supplemental and 16 complementary and compelling. 17 Q. Have you ever cited an 18 abstract in any published article of 19 yours? 20 A. Yes, I have. 21 Q. Are you an expert in the 22 kinds of testing that Dr. Saed has 23 reported in the materials you reviewed? 24 A. Yes, I am.</p>	<p style="text-align: right;">Page 376</p> <p>1 just? 2 BY MR. HEGARTY: 3 Q. Ovarian epithelial -- thank 4 you. 5 Have you ever done studies 6 using any type of ovarian epithelial cell 7 lines? 8 A. I have not. 9 Q. Have you ever done any study 10 using ovarian cancer cell lines? 11 A. I have not. Not personally. 12 Q. What data shows that the 13 doses that Dr. Saed used in his studies 14 are comparable to those to which 15 epithelial ovarian cells would be exposed 16 to via perineal application of talc? 17 MS. O'DELL: Objection to 18 form. 19 THE WITNESS: There was no 20 comparison in his study directly. 21 But if I may, I just want to say, 22 when you're looking at biological 23 plausibility, which was the 24 question that I was asked,</p>
<p style="text-align: right;">Page 375</p> <p>1 Q. Do you understand that 2 Dr. Saed is an expert for the plaintiffs 3 in this litigation? 4 A. I do understand that from 5 looking at his publication. 6 Q. Did you do anything yourself 7 to verify the reliability of the testing 8 that he performed whose results you have 9 read in his publications? 10 A. I focused my review and 11 reading of the study design, which is -- 12 and the experimental approach, which are 13 key factors for evaluating any study. 14 And I agree with the experimental 15 approach and the study design that he 16 used. 17 He used proper controls. He 18 used a dose-response. He used the proper 19 techniques in analyzing for cell 20 survivability as well as for oxidative 21 stress and gene expression changes. 22 Q. Have you ever done studies 23 using epithelial cell lines? 24 MS. O'DELL: Ovarian or</p>	<p style="text-align: right;">Page 377</p> <p>1 oftentimes higher doses in vitro 2 studies are used to provide a 3 mechanism or a plausibility or 4 feasibility that that can -- that 5 that product, in this case, talcum 6 powder product, can induce 7 inflammation, inflammatory 8 responses and changes in 9 antioxidant levels. 10 So it is not uncommon to use 11 higher doses in in vitro studies 12 than what might be seen in a human 13 for biological plausibility 14 studies. 15 BY MR. HEGARTY: 16 Q. Can you cite any study that 17 has shown the results reported in 18 Dr. Saed's studies in vivo in women using 19 talc? 20 MS. O'DELL: Objection to 21 form. 22 THE WITNESS: May I get 23 Dr. Saed's paper? 24 BY MR. HEGARTY:</p>

<p style="text-align: right;">Page 378</p> <p>1 Q. Well, I'm actually not 2 asking about Dr. Saed's paper. 3 A. Okay. 4 Q. But my question is -- you've 5 read Dr. Saed's papers, correct? 6 A. Yes, I have. 7 Q. Can you cite for me any 8 study that has shown the results he 9 reports in his studies in women using 10 talc? 11 MS. O'DELL: Object to form. 12 THE WITNESS: His studies 13 were in vitro studies. 14 BY MR. HEGARTY: 15 Q. Are there any such studies 16 looking at the effects in vivo of talc? 17 MS. O'DELL: Objection. 18 THE WITNESS: In vivo in 19 humans or in vivo in animals? 20 BY MR. HEGARTY: 21 Q. In humans. 22 MS. O'DELL: Object to the 23 form. 24 THE WITNESS: When you refer</p>	<p style="text-align: right;">Page 380</p> <p>1 polymorphisms? 2 A. I need to look at my CV 3 again, as being co-investigator. I've 4 worked with other people. I have not 5 performed studies looking at single 6 nucleotide polymorphisms. But I have 7 worked with people who have -- have done 8 them. And if I look at my curriculum 9 vitae, I can tell you if I've been on any 10 publications. 11 Q. Okay. Because of time, just 12 sitting here today, recognizing for the 13 record you haven't looked at your CV, do 14 any such studies come to mind? 15 A. I don't -- I have not done 16 those studies in my own laboratory. 17 Although I'm -- I'm just saying that I 18 may have been on a publication where 19 colleagues of mine have used that -- that 20 method, those methods. 21 Q. Do you have an opinion about 22 talc in single nucleotide polymorphisms 23 or SNPs? 24 MS. O'DELL: Objection.</p>
<p style="text-align: right;">Page 379</p> <p>1 to such studies, can you tell me 2 which studies -- which types of 3 studies again are you referring 4 to? 5 BY MR. HEGARTY: 6 Q. The cell studies that you 7 reference by Dr. Saed on Page 25 of your 8 report. 9 A. And the question is are 10 there any? 11 Q. Studies in humans showing 12 such effects following application of 13 talc to the perineum. 14 MS. O'DELL: Objection to 15 form. 16 THE WITNESS: Not to my 17 knowledge. 18 Excuse me. You said that 19 was on Page 25 that you were 20 referring to? 21 BY MR. HEGARTY: 22 Q. Correct. 23 Have you ever published a 24 paper discussing single nucleotide</p>	<p style="text-align: right;">Page 381</p> <p>1 THE WITNESS: I think 2 there -- there is literature 3 showing, including in Dr. Saed's 4 papers, that there are single -- 5 and in -- in a paper that looked 6 at women and looked at antioxidant 7 enzymes and they showed there was 8 single nucleotide polymorphism 9 changes in those women. 10 Looking at, I think it was 11 glutathione S-transferase M 1. 12 So what is my -- so if your 13 question is what is my opinion on 14 single nucleotide polymorphisms in 15 ovarian cancer? 16 BY MR. HEGARTY: 17 Q. Well, let me ask a different 18 question. Is your biologic mechanism -- 19 I'm sorry. Is your biologic plausibility 20 opinion between talc and ovarian cancer 21 the process or action that Dr. Saed 22 describes in his studies? 23 A. I believe that it could be 24 adding to the -- the plausibility of the</p>

<p style="text-align: right;">Page 382</p> <p>1 relationship or of the causation between 2 ovarian cancer and talcum powder 3 products. 4 Q. Well, is it your opinion 5 that the mechanism by which talc can be 6 biologically -- be a biological plausible 7 cause of ovarian cancer, that's cited by 8 Dr. Saed in his cell studies? 9 MS. O'DELL: Objection to 10 form. 11 THE WITNESS: I believe 12 that -- in my opinion and what I'm 13 stating here in the report, is 14 that inflammation is the 15 primary -- one of the primary 16 biological mechanisms. 17 Whether it appears from the 18 literature that single nucleotide 19 polymorphisms may, in fact, play a 20 role. 21 BY MR. HEGARTY: 22 Q. Okay. But is -- is that -- 23 is it your opinion that -- not that they 24 play -- just that they play a role, but</p>	<p style="text-align: right;">Page 384</p> <p>1 topic. I'll introduce the topic each 2 time that I ask you a question. 3 Going back to the Canadian 4 health assessment that you provided to us 5 at the beginning of the day. 6 A. Yes. 7 (Brief interruption.) 8 BY MR. HEGARTY: 9 Q. Doctor, we talked earlier 10 about Canada's health assessment with 11 regard to talc. Are you familiar with 12 the process by which the Canadian 13 authorities do that health assessment? 14 A. I am -- only from what is in 15 the document. 16 Q. Have you ever been a part of 17 that, of a Canadian health assessment 18 like the one shown with talc? 19 A. I've worked with Health 20 Canada. 21 Q. Okay. Have you ever worked 22 with Health Canada on doing a health 23 assessment like that reflected in the 24 document we looked at earlier today?</p>
<p style="text-align: right;">Page 383</p> <p>1 that is the mechanism for biologic 2 plausibility between talc and ovarian 3 cancer? 4 A. I -- I do not believe it 5 is -- it is not my opinion that -- it is 6 my opinion that single nucleotide 7 polymorphisms, along with inflammation 8 and -- and perhaps other mechanisms may 9 be involved that talc is associated with. 10 I focused my -- my opinion 11 on the assessment of inflammation and its 12 role. 13 MR. HEGARTY: Off the record 14 for a minute. 15 THE VIDEOGRAPHER: The time 16 is 4:48 p.m. We are off the 17 record. 18 (Short break.) 19 THE VIDEOGRAPHER: We are 20 back on the record. The time is 21 5:08 p.m. 22 BY MR. HEGARTY: 23 Q. Dr. Zelikoff, I'm going to 24 jump around a little bit from topic to</p>	<p style="text-align: right;">Page 385</p> <p>1 A. No, I have not. 2 Q. Do you know what kind of 3 standards that they apply in determining 4 whether to call -- whether to say whether 5 there's a potential for harm with a 6 substance? 7 A. Just what is in the 8 document. And then I use my own 9 professional judgment, whether I agree 10 with that or not. 11 Q. Did plaintiff's counsel 12 provide you with some scientific and 13 medical literature with regard to talc or 14 ovarian cancer? 15 A. So the question is whether I 16 was provided with some scientific and 17 medical literature with regard -- yes, 18 many of the articles in the binders were 19 provided to me by them. 20 Q. Are you able to identify 21 which of those articles came from 22 plaintiffs' counsel versus which you 23 found on your own? 24 A. I may be able to do that</p>

<p style="text-align: right;">Page 386</p> <p>1 with some, yes. But this is over a 2 period of, as I said, 2017 to now. 3 Q. With regard to your 4 invoices -- do you have your invoices 5 there? 6 A. I do not. 7 Q. They've been marked as an 8 exhibit. 9 A. Oh. 10 Q. Can someone help her find 11 those invoices? 12 MS. O'DELL: Did you take 13 them back? I don't know that -- 14 there was only one copy. 15 MR. HEGARTY: I don't think 16 I did. I think it was Exhibit 1. 17 MS. O'DELL: The reason I 18 say that is I did not see it 19 during the lunch break when I 20 looked at -- 21 THE WITNESS: I do have the 22 invoices in my binder here. 23 BY MR. HEGARTY: 24 Q. Okay. If you can turn to</p>	<p style="text-align: right;">Page 388</p> <p>1 Q. What are the differences 2 between your current report dated 3 November 16, 2018, and the final report 4 that you provided as shown here back in 5 February of 2018? 6 A. It was -- I own that. It 7 should have said draft report. And the 8 difference is that that's more literature 9 and more time had gone by for the 10 emergence and review of more literature. 11 Q. You go from a reference on 12 February 4, 2018, to the next reference 13 on September 20th -- I'm sorry. Did I 14 say -- let me back up. 15 You go from a reference on 16 February 4, 2018, to the next cite for 17 time on September 20, 2018. Did you 18 review any additional literature between 19 February 4th and September 20, 2018? 20 A. Yes, I'm sure I did. And I 21 also reviewed the production documents 22 within that time. More of the production 23 documents. 24 Q. Your report doesn't show any</p>
<p style="text-align: right;">Page 387</p> <p>1 your binder, please. 2 A. If I recall. 3 Q. If we can find that exhibit, 4 that would be helpful? 5 MS. O'DELL: I'm not sure 6 there are any invoices in her 7 binder. 8 Is it in the stack that's 9 right there? 10 MR. HEGARTY: No, I don't 11 think so. 12 BY MR. HEGARTY: 13 Q. Yeah invoices. I found it. 14 Your invoices, Doctor, 15 reflect that you prepared a final report 16 delivered on February 4, 2018. 17 Do you see that? 18 A. I do see that. 19 Q. That was almost a year ago, 20 correct? 21 MS. O'DELL: Objection to 22 form. 23 THE WITNESS: Yes. 24 BY MR. HEGARTY:</p>	<p style="text-align: right;">Page 389</p> <p>1 time invoiced between February 4, 2018, 2 and September 20, 2018. Did you spend 3 time reviewing literature or otherwise 4 working on your report that's not 5 contained in your invoices? 6 A. It -- I may have. I did not 7 always invoice for something that I spent 8 maybe an hour on. 9 Q. Are you able to cite for me 10 the sections in your report that you 11 added or changed between the report that 12 you prepared on February 4, 2018, and the 13 November 16, 2018, report? 14 A. Not without seeing both 15 reports side by side. 16 Q. Do you still have a copy of 17 the February 4, 2018, report? 18 A. Not with me. 19 Q. Does it exist? 20 A. It likely does on my 21 computer, yes. 22 Q. You mentioned that you 23 referred to -- that you reviewed Julie 24 Pier's deposition testimony?</p>

<p style="text-align: right;">Page 390</p> <p>1 A. I said three-quarters of the 2 deposition, half to three-quarters. 3 Q. That was provided to you by 4 counsel for plaintiffs, correct? 5 A. Yes, correct. 6 Q. Do you know how they went 7 about selecting the deposition 8 transcripts to provide to you for 9 purposes of your review in this case? 10 A. I do not. 11 Q. Did you ask for any 12 deposition -- did you ask for the 13 depositions of all experts who have 14 testified in this litigation? 15 MS. O'DELL: Objection to 16 form. 17 THE WITNESS: I did not ask 18 for depositions. 19 Let me -- let me retract 20 that, please. If in reading my 21 literature there was something 22 that I thought might be in a 23 deposition of someone, I asked the 24 plaintiff attorneys if they had</p>	<p style="text-align: right;">Page 392</p> <p>1 Canada, like Exhibit Number 9? 2 A. I'm sorry. 3 MS. O'DELL: Objection to 4 form. 5 THE WITNESS: All I can say 6 is that in working with Health 7 Canada on immunology in my early 8 career days, that I may have used 9 an assessment like that. 10 BY MR. HEGARTY: 11 Q. Can you cite for me, sitting 12 here today, anytime that you -- your 13 opinions were informed by a Health Canada 14 safety assessment or screening 15 assessment? 16 MS. O'DELL: Object to the 17 form. Other than what she said? 18 THE WITNESS: Except for 19 what I said, I cannot recall. 20 BY MR. HEGARTY: 21 Q. Did you review for purposes 22 of your opinions in this case the current 23 National Cancer Institutes position -- 24 healthcare -- healthcare -- health</p>
<p style="text-align: right;">Page 391</p> <p>1 anything in that regard that would 2 lend to my opinion. 3 BY MR. HEGARTY: 4 Q. And did you ever ask for any 5 additional depositions beyond those that 6 were provided? 7 A. No, I did not. 8 Q. Going back to the Health 9 Canada assessment. Have you ever cited 10 to a Health Canada assessment in any 11 written publication of yours? 12 A. Without looking at my 13 publications, I cannot. But I can tell 14 you that coming to mind just sitting 15 here, as I said, I worked with Health 16 Canada, and I worked with them on my 17 research in fish immunology, and it is 18 possible that I cited Health Canada -- 19 Health Canada literature in those 20 publications concerning fish. 21 Q. Sitting here today, can you 22 recall at any point in time when you -- 23 when your opinions were informed by a 24 draft screening assessment by Health</p>	<p style="text-align: right;">Page 393</p> <p>1 professional PDQ, or the NCI PDQ? 2 A. I have seen that recently. 3 Q. I'll mark as Exhibit Number 4 23, a copy of the NCI PDQ that mentions 5 talc. 6 (Document marked for 7 identification as Exhibit 8 Zelikoff-23.) 9 BY MR. HEGARTY: 10 Q. Have you seen what I marked 11 as Exhibit 23 before -- or as of the time 12 that you drafted your report? 13 A. No, sir. 14 Q. Plaintiffs' counsel did not 15 provide you a copy of that? 16 A. Not prior to my report, no. 17 Q. How did you happen -- who -- 18 strike that. 19 Did -- from where did you 20 receive a copy of Exhibit 23 after 21 preparing your report? 22 A. From the plaintiff attorney. 23 Q. Did you ask for it? 24 A. In general, I asked for all</p>

<p style="text-align: right;">Page 394</p> <p>1 relevant literature and internal 2 information. But I did not specifically 3 ask for the NCI report. 4 Q. When you asked for all 5 relevant information, internal 6 information, was that prior to preparing 7 your expert report? 8 A. That's pretty much on a 9 chronic level, in other words from the 10 time that I was recruited or asked to 11 participate in this, I always asked, "Is 12 there literature? Is there more 13 literature? Here is the literature that 14 I have found," which were quite a number. 15 "Is there anything else that you can add 16 to this?" So I provided literature, and 17 they provided me with literature. 18 Q. You did not find the NCI's 19 PDQ yourself? 20 A. I did not find it myself. 21 Q. Did the NCI PDQ statements 22 on perineal talc exposure inform your 23 opinions in this case? 24 A. As I said, I only saw it</p>	<p style="text-align: right;">Page 396</p> <p>1 A. I reviewed their opinions. 2 I have many questions about how they 3 reached their opinions and what studies 4 they used. 5 If we can just be on the 6 same page in terms of what their opinion 7 is? 8 Q. I'm looking at the section 9 under perineal talc exposure. And my -- 10 my question is -- strike that. 11 I'm looking at the section 12 on perineal talc exposure which is about 13 four pages from the end. 14 A. I see. 15 Q. And my question is only 16 whether that section informed your 17 opinions in this case. 18 MS. O'DELL: Object to the 19 form. 20 THE WITNESS: I reviewed it. 21 It did not change my opinion. 22 Did -- did it inform my opinion? 23 It did not change my opinion. 24 BY MR. HEGARTY:</p>
<p style="text-align: right;">Page 395</p> <p>1 within the last few days. 2 Q. Understood. But you also 3 reviewed the Saed manuscript, you 4 reviewed the Canadian health assessment. 5 You said both those documents informed 6 your opinions. 7 So my question is, did the 8 NCI PDQ also inform your opinions. 9 MS. O'DELL: Object to the 10 form. 11 THE WITNESS: Well, the -- 12 the documents that you previously 13 mentioned do not inform my opinion 14 prior to my report of 15 November 16th. However, it's 16 information that has added to me 17 to get to this place where I am 18 right now. 19 So my opinion has not 20 changed from my report until 21 sitting here today. 22 BY MR. HEGARTY: 23 Q. Did the NCI PDQ add to your 24 opinions in this case?</p>	<p style="text-align: right;">Page 397</p> <p>1 Q. Do you agree with the NCI 2 PDQ statement on perineal talc exposure? 3 A. If we are talking about 4 their final conclusion? 5 Q. I'm talking -- yes. We can 6 talk about their final conclusion. 7 A. Okay. If I'm recalling 8 this, their final conclusion that -- was 9 that there was no causal relationship 10 between talc -- talcum powder exposure 11 and ovarian cancer. Is that -- 12 Q. Well, the -- the weight of 13 the evidence does not support an 14 association between perineal talc 15 exposure and an increased risk of ovarian 16 cancer. Do you agree with that 17 statement? 18 A. I do not agree with that 19 statement. 20 And I find, in reading this 21 document, that I'm not sure how they 22 reached that conclusion. On several 23 points, if you're interested. 24 One is --</p>

<p style="text-align: right;">Page 398</p> <p>1 Q. No, I'm just asking you 2 whether you agreed with it. 3 A. I do not agree with their 4 final conclusion. 5 Q. Neither FDA nor any 6 scientific regulatory or other group has 7 ever sought out your opinions with regard 8 to the biologic plausibility of talc and 9 ovarian cancer, correct? 10 A. That is correct. 11 Q. You made reference earlier 12 to the Penninkilampi article. Do you 13 recall that? 14 A. I recall mentioning it, yes. 15 Q. I'm going to mark as 16 Exhibit 34 a copy of the Penninkilampi 17 article. That's the article that you 18 were talking about earlier, correct? 19 A. 2018, correct. 20 (Document marked for 21 identification as Exhibit 22 Zelikoff-34.) 23 BY MR. HEGARTY: 24 Q. If you turn over to page --</p>	<p style="text-align: right;">Page 400</p> <p>1 A. Yes, I do. 2 Q. Third line down it says, 3 "The mechanism by which perineal talc use 4 may increase the risk of ovarian cancer 5 is uncertain." 6 Do you agree with that 7 statement? 8 MS. O'DELL: Objection to 9 form. 10 THE WITNESS: I think 11 there's no -- in providing 12 biological plausibility, 13 biological plausibility, in and of 14 itself, says that there is a 15 possible mechanism or action that 16 could provide evidence for the 17 causation. 18 So the mechanism by which 19 perineal talc use may increase the 20 risk of ovarian cancer is 21 uncertain. It does not mean 22 it's -- it means it's uncertain, 23 that there are many viewpoints on 24 it.</p>
<p style="text-align: right;">Page 399</p> <p>1 strike that. 2 This is an article that you 3 rely on for purposes of your opinions in 4 this case, correct? 5 A. This is an article that I 6 reviewed and played into, yes, informed 7 my opinions. 8 Q. Did you find it to be a 9 reliable source of information? 10 MS. O'DELL: Object to the 11 form. 12 THE WITNESS: I found no 13 problems in the study design as I 14 read it. 15 Again, I'm not an 16 epidemiologist. So getting into 17 the nuances of this. I'm a 18 toxicologist and I depend on my 19 epidemiology colleagues to fill in 20 the gaps. 21 BY MR. HEGARTY: 22 Q. Over on Page 45, under the 23 section Discussion. Do you see that 24 section?</p>	<p style="text-align: right;">Page 401</p> <p>1 BY MR. HEGARTY: 2 Q. At the very -- in the very 3 last line of that article -- I'm sorry, 4 the very last line of that paragraph it 5 says, "The potential mechanism by which 6 genital talc is associated with an 7 increased risk of ovarian cancer hence 8 remains unclear." 9 Do you agree with that 10 statement? 11 A. I think there is -- in -- in 12 regards to your previous questions that 13 asked me if it was -- if there was an 14 agreement among the medical population, 15 and I said that I didn't know that there 16 was agreement or was not agreement. I 17 thought that there were not agreement. 18 So I agree with the statement that there 19 is still room for further study. 20 Unclear does not mean 21 unknown or that there are not biological 22 plausible mechanisms that could be 23 entertained. 24 Q. Is inflammation part of a</p>

<p style="text-align: right;">Page 402</p> <p>1 normal mechanism of response to the 2 presence of particles in the lungs? 3 A. Depending upon the particle, 4 inflammation can be a normal part of a 5 response, yes. 6 Q. Can tumors occur in the 7 respiratory system with very high 8 exposure to particles that overwhelm the 9 body's clearance mechanisms and lead to 10 particle overload of lung macrophages? 11 A. Are you referring to the NTP 12 study? 13 Q. I'm not referring to any 14 study in particular. That was just a 15 question in general. 16 A. Okay. Can you repeat the 17 question? 18 Q. Yeah. Can tumors occur in 19 the respiratory system with very high 20 exposure to particles that overwhelm the 21 body's clearance mechanisms and lead to 22 particle overload of lung macrophages? 23 MS. O'DELL: Object to form. 24 THE WITNESS: That is a --</p>	<p style="text-align: right;">Page 404</p> <p>1 statement in the third paragraph at the 2 end that says even incidental -- the 3 third paragraph at the end. 4 A. I was looking for a pen. 5 Excuse me. 6 Okay. Go ahead. 7 Q. Says, "Even incidental 8 contamination by amphibole forms of 9 asbestos is hazard enough to cause 10 asbestos-related illnesses." 11 Do you see where I'm 12 reading? 13 A. I'm sorry, are you in the 14 first paragraph? 15 Q. Third paragraph. 16 A. Third paragraph. 17 Q. At the end. 18 A. At the -- traces of these 19 types of asbestos are -- 20 Q. No, third paragraph. 21 Even -- the last line. "Even incidental 22 contamination by amphibole forms of 23 asbestos is hazard enough to cause 24 cancer-related illnesses."</p>
<p style="text-align: right;">Page 403</p> <p>1 that has been seen as a 2 potential -- as a potential to 3 occur, yes. 4 BY MR. HEGARTY: 5 Q. Are there any publications 6 that indicate such a mechanism of 7 particle overload can occur in the 8 ovaries? 9 MS. O'DELL: Objection to 10 form. 11 THE WITNESS: No studies 12 that I'm aware of that -- that 13 refer to particle overload in the 14 ovaries in this regard, in regard 15 to talcum powder. There's 16 evidence, of course, as I said 17 that there is talcum powder in the 18 ovary. 19 BY MR. HEGARTY: 20 Q. Over on Page 5 of your 21 report, Exhibit 2. 22 A. Page headed by Section 4, 23 Asbestos? 24 Q. Correct. You make a</p>	<p style="text-align: right;">Page 405</p> <p>1 Do you see where I'm 2 reading? 3 A. Says, "Cause 4 asbestos-related illnesses." 5 Q. I'm sorry. "Can cause 6 asbestos-related illnesses." You cite -- 7 A. I see where you are reading. 8 Q. -- the Rohl and Langer 9 paper? 10 A. Yes. 11 Q. I'll mark as Exhibit 35 the 12 Rohl and Langer paper that you've cited. 13 (Document marked for 14 identification as Exhibit 15 Zelickoff-35.) 16 BY MR. HEGARTY: 17 Q. Doctor, nowhere in that 18 paper did the author say that incidental 19 contamination by amphibole forms of 20 asbestos is hazard enough -- hazardous 21 enough to cause asbestos-related 22 illnesses, do they? 23 MS. O'DELL: Objection to 24 form.</p>

<p style="text-align: right;">Page 406</p> <p>1 THE WITNESS: I'm sorry, I'm 2 not certain that this is the same 3 paper. This is Rohl, et al. The 4 paper that I cited is Rohl and 5 Langer. 6 BY MR. HEGARTY: 7 Q. It's dated 1976 -- 8 A. 1976. 9 Q. -- correct? 10 A. That's correct. 11 Q. If you look in the abstract 12 of that paper -- 13 A. Yes. The paper -- 14 Q. -- the paper that I marked 15 as Exhibit 35. 16 A. Rohl, et al, yes. 17 Q. Yes. It says, "It's 18 possible adverse health effects from 19 intermittent use of these products, 20 especially those that contain asbestiform 21 and fragmented anthophyllite, tremolite, 22 chrysotile, quartz, and trace minerals 23 are presently unknown and warrant 24 evaluation."</p>	<p style="text-align: right;">Page 408</p> <p>1 Many investigators, 2 including myself, have papers that come 3 out the same year but with different 4 authors. 5 Q. If you -- you turn over to 6 Page 6 of your report. 7 A. Yes, sir. 8 Q. At the end of the first 9 paragraph, at the top of the page. 10 A. Yes. 11 Q. You say that "the close 12 proximity of asbestos in talc and mineral 13 deposits makes extraction of either 14 material alone difficult, if not 15 impossible." 16 Do you see where I'm 17 reading? 18 A. Yes, I do. 19 Q. Is it your testimony that it 20 is impossible to extract talc from 21 mineral deposits without asbestos? 22 MS. O'DELL: Objection to 23 form. 24 THE WITNESS: I'm not a --</p>
<p style="text-align: right;">Page 407</p> <p>1 Did I read that correctly? 2 A. I'm sorry, you are in the 3 abstract, but I don't know what line you 4 are on. 5 Q. The very last line of the 6 abstract. 7 A. "Possible adverse health 8 effects from intermittent use of these 9 products especially those that contain 10 asbestiform and fragmented anthophyllite, 11 tremolite, chrysotile, quartz, and trace 12 minerals are presently unknown and 13 warrant evaluation." 14 Yes. This is also dated 15 1976. 16 Q. Which is the date that you 17 cite to the Rohl and Langer paper? 18 A. Yes, I -- I understand that, 19 sir. However, because this is a Rohl et 20 al., it is certainly possible that I 21 miscited and it was Rohl et al. But my 22 citation in there is Rohl and Langer. So 23 it may have been an error on my part. 24 However, there's pause.</p>	<p style="text-align: right;">Page 409</p> <p>1 I'm not a geologist. I cannot -- 2 I can only rely on the references 3 that are there. 4 BY MR. HEGARTY: 5 Q. Can you list all the steps 6 used in the processing of pharmaceutical 7 grade talc? 8 A. I can give you an overview. 9 But again, I'm not a commercial talc 10 production person, nor am I a geologist, 11 nor am I in the industry. So I can only 12 give you a superficial glimpse. 13 Q. Can you describe the 14 beneficiation for talc? 15 MS. O'DELL: Objection to 16 form. Asked and answered. 17 THE WITNESS: Not in -- not 18 in detail. I only know in general 19 that there is -- actually, I 20 prefer not to answer that at all 21 because I don't want to be 22 inaccurate. It's not my field. 23 BY MR. HEGARTY: 24 Q. Can you turn over to Page 7</p>

<p style="text-align: right;">Page 410</p> <p>1 of your report.</p> <p>2 In the second paragraph you</p> <p>3 refer to the deposition of Alice Blount.</p> <p>4 Do you see that?</p> <p>5 A. Yes, I do. Second sentence.</p> <p>6 Q. And you contend that the</p> <p>7 sample she tested claimed to include</p> <p>8 asbestos, including asbestos in Johnson's</p> <p>9 Baby Powder. Do you see where you make</p> <p>10 that reference?</p> <p>11 A. Yes, I'm citing her</p> <p>12 deposition.</p> <p>13 Q. Did you read the entirety of</p> <p>14 her deposition?</p> <p>15 A. No, sir.</p> <p>16 Q. What testing method did she</p> <p>17 use?</p> <p>18 A. I'd like to see the</p> <p>19 deposition again.</p> <p>20 Q. Did you see from her</p> <p>21 deposition where she testified that her</p> <p>22 results published in 1991 came from a</p> <p>23 Johnson's Baby Powder bottle purchased in</p> <p>24 1996?</p>	<p style="text-align: right;">Page 412</p> <p>1 Q. You read every word of it?</p> <p>2 A. I reviewed it. And I read</p> <p>3 it to the best of my ability.</p> <p>4 Q. You make reference there to</p> <p>5 Exhibits 47 and 28, 47 from Julie Pier</p> <p>6 deposition and 28 from Dr. Hopkins'</p> <p>7 deposition.</p> <p>8 Do you see that?</p> <p>9 A. Yes, I do.</p> <p>10 Q. Do you know who prepared</p> <p>11 those exhibits?</p> <p>12 A. I do not. I would make an</p> <p>13 assumption that it was attorneys.</p> <p>14 Q. Were you aware that they</p> <p>15 were prepared by counsel for plaintiffs?</p> <p>16 MS. O'DELL: Objection to</p> <p>17 form.</p> <p>18 THE WITNESS: As the</p> <p>19 questions were asked by some of</p> <p>20 the attorneys for the plaintiff, I</p> <p>21 would make that assumption.</p> <p>22 BY MR. HEGARTY:</p> <p>23 Q. Did you do anything yourself</p> <p>24 to verify the accuracy of the information</p>
<p style="text-align: right;">Page 411</p> <p>1 A. You know, I'm waiting for</p> <p>2 the -- see the article, please.</p> <p>3 Q. Let me withdraw the</p> <p>4 question. I don't have time to cover</p> <p>5 that.</p> <p>6 If you turn over to -- if</p> <p>7 you look at Page 7, the second-to-last</p> <p>8 paragraph you make reference there to the</p> <p>9 testimony of Dr. Hopkins and the</p> <p>10 testimony of Julie Pier.</p> <p>11 Do you see that?</p> <p>12 A. I see reference to</p> <p>13 Dr. Hopkins in the third sentence. And</p> <p>14 in the same paragraph, I see on the last</p> <p>15 sentence, deposition of Julie Pier,</p> <p>16 corporate representative of Imerys.</p> <p>17 Q. You've already testified</p> <p>18 that you have not completed reading the</p> <p>19 deposition of Julie Pier, correct?</p> <p>20 A. I have testified to that,</p> <p>21 yes.</p> <p>22 Q. Did you read the entirety of</p> <p>23 the deposition of Dr. Hopkins?</p> <p>24 A. I read the entirety, yes.</p>	<p style="text-align: right;">Page 413</p> <p>1 in any of those exhibits?</p> <p>2 A. I'm not sure what you mean</p> <p>3 did I do anything myself. I read them,</p> <p>4 and I did not do any further literature</p> <p>5 searching, if that's what you mean.</p> <p>6 Q. Did you review the test</p> <p>7 results themselves that are supposedly</p> <p>8 reported in those two exhibits?</p> <p>9 MS. O'DELL: Objection to</p> <p>10 form.</p> <p>11 THE WITNESS: Did I review</p> <p>12 the testing methodology? I did</p> <p>13 not review it in the sense that I</p> <p>14 did further literature searching,</p> <p>15 but I -- I looked at and reviewed</p> <p>16 the testing methods that they --</p> <p>17 that they said they used.</p> <p>18 BY MR. HEGARTY:</p> <p>19 Q. Did you actually pull the</p> <p>20 tests that are referenced in those</p> <p>21 exhibits and look at the test results</p> <p>22 yourself?</p> <p>23 A. I did not.</p> <p>24 Q. Are you aware that in 2009</p>

<p style="text-align: right;">Page 414</p> <p>1 FDA pulled -- did its own testing with 2 regard to asbestos and talc? 3 A. I am aware of that. 4 Q. Did you review the results 5 of those tests? 6 A. I did review the results. 7 It doesn't come to mind right now. I'd 8 like to see a copy of it, if I may. 9 Q. Nowhere in your report do 10 you cite those test results, do you? 11 A. Not that I can recall. 12 I do cite a paper or a 13 comment by Epstein writing to the FDA in 14 here. And the FDA's response in terms of 15 migration. 16 But in answer to your 17 question -- can you repeat your question? 18 Q. Sure. Did you cite -- you 19 agree that you didn't cite anywhere -- 20 strike that. 21 You did not cite anywhere in 22 your report the results of the FDA's 23 testing of talc in 2009, correct? 24 A. It doesn't appear so, no.</p>	<p style="text-align: right;">Page 416</p> <p>1 THE WITNESS: There are many 2 studies that IARC used, not just 3 worker study populations. 4 BY MR. HEGARTY: 5 Q. But their conclusion with 6 regard to designating talc -- sorry, 7 designating asbestos as Category 1 was 8 based on five cohort studies involving 9 heavy industrial exposure, correct? 10 A. The preponderance -- or the 11 weight -- the weight of evidence was 12 contributed among all studies, but it's 13 my -- it's my thought that the worker 14 studies were probably weighted as heavy 15 as any others. 16 Q. You agree -- you agree that 17 nowhere in your report do you analyze 18 what asbestos exposure levels had been 19 shown to induce a biologically plausible 20 effect in tissues, correct? 21 MS. O'DELL: Object to the 22 form. 23 THE WITNESS: Again, what do 24 you mean by analyze?</p>
<p style="text-align: right;">Page 415</p> <p>1 Q. Did you have that 2 information before you finalized your 3 report? 4 A. I'm not certain. Probably 5 yes. 6 Q. Did you review all the 7 epidemiologic literature looking at 8 asbestos exposure and ovarian cancer? 9 A. Well, as I said, I'm not an 10 epidemiologist. So I looked at several 11 of the meta-analyses, including 12 Dr. Taher. 13 Q. Did you read all the 14 meta-analyses that had been published 15 with regard to asbestos and ovarian 16 cancer? 17 A. No, I have not. 18 Q. The medical literature 19 looking at asbestos exposure and ovarian 20 cancer was based on exposure to -- was 21 based on a heavy industrial exposure, 22 correct? 23 MS. O'DELL: Objection to 24 form.</p>	<p style="text-align: right;">Page 417</p> <p>1 BY MR. HEGARTY: 2 Q. Well, nowhere do you cite 3 studies in your report reporting on the 4 effect of asbestos in tissues, correct? 5 A. I certainly do talk about 6 asbestos. If you give me a minute to 7 review. 8 I talk about it on Page 7 9 being listed as a Group 1 carcinogen. 10 Q. My question is nowhere in 11 your report do you analyze the studies 12 that look at the toxicity or discuss the 13 toxicity of asbestos in human tissue, 14 correct? 15 MS. O'DELL: Object to the 16 form. 17 THE WITNESS: I -- I did not 18 look at -- I did not analyze in 19 depth, no, the studies that are 20 associated with the IARC report, 21 if that's what you're asking. 22 BY MR. HEGARTY: 23 Q. What type of chromium -- 24 strike that.</p>

<p style="text-align: right;">Page 418</p> <p>1 Is chromium-6 in Johnson's 2 Baby Powder? 3 A. Chromium is in Johnson's 4 Baby Powder. 5 Q. I'm sorry? 6 A. Chromium is present. 7 Q. Is chromium-6 present in 8 Johnson's Baby Powder? 9 A. There are indications. They 10 just discuss total chromium. 11 Q. Can you testify here today 12 that Johnson's Baby Powder has chromium-6 13 in it? 14 MS. O'DELL: Object to the 15 form. 16 THE WITNESS: Again, not 17 being a geologist and only going 18 by the internal documents, and if 19 I may also look at one of the 20 exhibits that has the data for the 21 metals. I'm sorry. 22 MS. O'DELL: It's Exhibit C 23 that was marked. 24 THE WITNESS: I don't want</p>	<p style="text-align: right;">Page 420</p> <p>1 Q. Of your report. The third 2 paragraph from the bottom where it 3 begins, "Chromium-3." 4 A. Yes. 5 Q. You say, "Chromium-3 has 6 weak cell membrane permeability, allowing 7 it to cross the cell membrane in order to 8 bind to DNA and cause lesions." That's 9 not correct, is it? 10 A. That is not correct. That 11 is an error on my part in the report. 12 Chromium-3 has strong membrane 13 permeability. And when you asked me the 14 question initially whether there was an 15 error in my report, I should have looked 16 at it, and that is an error. Yes. 17 Q. In fact chromium-3 does not 18 cross the cell membrane, correct? It's 19 unable to cross the cell membrane? 20 A. Chromium-6 crosses the cell 21 membrane and then converts into -- is 22 oxidized to chromium-3. And chromium-3 23 is the actual component which causes the 24 instability.</p>
<p style="text-align: right;">Page 419</p> <p>1 to go by my memory alone. I'd 2 like to see that. 3 Thank you very much. 4 In the document prepared as 5 Exhibit C, chromium has not been 6 speciated and it's listed as total 7 chromium. I would make the 8 assumption from my professional 9 opinion that in mining, you do get 10 both chromium-6 and chromium-3 11 when you have -- when you're 12 mining talc. But I'm not a 13 geologist. 14 BY MR. HEGARTY: 15 Q. Does chromium-6 only come 16 through industrial processing? 17 A. No. It can actually be 18 found in the soil as a product of 19 contamination. 20 Q. If you look over -- 21 A. And it can be re-oxidized. 22 Yes. 23 Q. If you look over on Page 9? 24 A. Of?</p>	<p style="text-align: right;">Page 421</p> <p>1 Q. But chromium-3 is unable to 2 cross the cell membrane, correct? 3 A. Completely. To some degree 4 it has -- it can cross to some -- some 5 minimal degree. But it's hexavalent 6 chromium which can cross -- which has 7 great capacity to cross the cell 8 membrane, yes. 9 May I take a minute, please. 10 Let me -- let me restate 11 based upon the third paragraph that 12 starts, "Chromium-3 has weak cell 13 membrane permeability." 14 It has weak to no cell 15 membrane permeability. 16 It is the active oxidized 17 product of hexavalent chromium or 18 chromium-6, that along with chromium-4 19 and chromium-5 which is responsible for 20 genetic instability and oxidative stress. 21 So it's chromium-3. 22 Q. If you turn over to Page 23 13 -- I'm sorry, Page 12 of your report. 24 Section entitled C, Fragrances?</p>

<p style="text-align: right;">Page 422</p> <p>1 A. Yes.</p> <p>2 Q. As of the time you prepared</p> <p>3 your report, your entire opinions with</p> <p>4 regard to fragrances was based on the</p> <p>5 report by Michael Crowley, correct?</p> <p>6 A. That is correct.</p> <p>7 Q. You understand --</p> <p>8 A. And, and what I know about</p> <p>9 some of the components from other --</p> <p>10 other studies.</p> <p>11 Q. Have you had any prior work</p> <p>12 experience with him?</p> <p>13 A. Dr. Michael Crowley?</p> <p>14 Q. Yes.</p> <p>15 A. No.</p> <p>16 Q. Do you know anything about</p> <p>17 his qualifications beyond -- beyond what</p> <p>18 you read in his report?</p> <p>19 A. No. Just in his report and</p> <p>20 the information that he gives about</p> <p>21 himself. And the questions that were</p> <p>22 asked to him and the responses.</p> <p>23 Q. You say that you concur --</p> <p>24 "I concur with his opinion." Does that</p>	<p style="text-align: right;">Page 424</p> <p>1 expert witness report in litigation?</p> <p>2 MS. O'DELL: Object to the</p> <p>3 form.</p> <p>4 THE WITNESS: I am trying to</p> <p>5 recall whether or not I have ever</p> <p>6 had that opportunity.</p> <p>7 BY MR. HEGARTY:</p> <p>8 Q. Sitting here right now, can</p> <p>9 you recall when you had such an</p> <p>10 opportunity?</p> <p>11 A. In this particular setting</p> <p>12 of being deposed?</p> <p>13 Q. Or in any -- in any setting</p> <p>14 where you are concurring with the opinion</p> <p>15 of someone who -- who comments on</p> <p>16 toxicity in an expert witness report</p> <p>17 written for litigation?</p> <p>18 MS. O'DELL: Objection to</p> <p>19 form.</p> <p>20 THE WITNESS: I would --</p> <p>21 I -- I would comment on it if I</p> <p>22 agreed.</p> <p>23 And in this case, you know,</p> <p>24 having the knowledge base that I</p>
<p style="text-align: right;">Page 423</p> <p>1 mean that you agreed with everything that</p> <p>2 he says in his report?</p> <p>3 MS. O'DELL: Object to the</p> <p>4 form.</p> <p>5 THE WITNESS: I concur with</p> <p>6 his statement which says that</p> <p>7 "some of these chemicals in</p> <p>8 fragrances may contribute to the</p> <p>9 inflammatory response, toxicity</p> <p>10 and potential carcinogenicity of</p> <p>11 Johnson & Johnson talcum powder</p> <p>12 products."</p> <p>13 And that's based on the</p> <p>14 knowledge of some of the chemicals</p> <p>15 as I said that I've reviewed for</p> <p>16 other studies and personal</p> <p>17 studies. And they are indeed</p> <p>18 inflammatory and can cause</p> <p>19 toxicity.</p> <p>20 BY MR. HEGARTY:</p> <p>21 Q. Prior to reading</p> <p>22 Dr. Crowley's report, had you ever</p> <p>23 concurred with a finding as to toxicity</p> <p>24 of a substance based on the reading of an</p>	<p style="text-align: right;">Page 425</p> <p>1 have, not on -- certainly not on</p> <p>2 all 150 different chemicals, which</p> <p>3 is why I did my own literature</p> <p>4 search, but on the chemicals that</p> <p>5 I do know, I did agree with the</p> <p>6 fact that they -- they do</p> <p>7 contribute to inflammatory</p> <p>8 responses, toxicity, some are</p> <p>9 cytotoxic and produce cell injury</p> <p>10 and potential carcinogenicity.</p> <p>11 So as ethyl benzene as one</p> <p>12 of the ingredients or one of the</p> <p>13 constituents in fragrances, is</p> <p>14 listed as a type -- as a Class 2</p> <p>15 carcinogen. So I did agree with</p> <p>16 it.</p> <p>17 If I had any question, I did</p> <p>18 my own search.</p> <p>19 BY MR. HEGARTY:</p> <p>20 Q. Over on page -- Pages 12 and</p> <p>21 13, again you discuss exposure routes of</p> <p>22 talc either through perineal exposure or</p> <p>23 through inhalation, correct? And that</p> <p>24 carries over to Pages 14 and 15, and 16</p>

<p style="text-align: right;">Page 426</p> <p>1 and 17. 2 A. Okay. 3 Q. So in that section, did you 4 in any way analyze whether the particles 5 that -- whether talc can transport in the 6 same way that the particles do in the 7 studies that you cite? 8 MS. O'DELL: Objection to 9 form. 10 BY MR. HEGARTY: 11 Q. In other words, did you cite 12 any authority showing that talc particles 13 transport in the same way as the 14 particles you reference in these studies? 15 A. Not conclusively. But as I 16 said, if the particles are of similar 17 sizes, which they are in these -- in 18 these animal studies, then I would have 19 no reason to believe that the talc 20 particles did not move in the same 21 manner. 22 Q. Well, do you agree that it 23 is important when talking about transport 24 of particles, that -- strike that. Let</p>	<p style="text-align: right;">Page 428</p> <p>1 that are applied to talc via the perineal 2 route? 3 A. What I did was I looked at 4 the internal documents, found that the -- 5 according to the -- the instrumentation 6 and the graphics that they did, as well 7 as Dr. Longo, and looked at the size 8 range of the particles. As I said, the 9 median and the average is around 10.5 to 10 11.5, but there were particle size range 11 in the talc -- talcum powder products 12 that range all the way from 50 microns or 13 larger all the way down to 0.3 microns or 14 300 nanometers. 15 Q. Well, did you do any 16 correlation to determine whether the -- 17 the size of the particles studied in 18 the -- in the articles you cite in any 19 way correlate or relate to the particle 20 sizes in Johnson's Baby Powder? 21 MS. O'DELL: Object to the 22 form. 23 THE WITNESS: The size of 24 particles that were used in many</p>
<p style="text-align: right;">Page 427</p> <p>1 me ask it a different way. 2 You cite to an authority 3 that makes the following statement, I 4 don't want to ask you -- I want to ask 5 you if you agree with it. 6 A. Okay. 7 Q. In an experiment to 8 evaluate -- 9 A. I'm sorry. What page? 10 Q. It's -- it's not on -- it's 11 not in your report. It's part of my 12 question. 13 A. Okay. 14 Q. Do you agree that in an 15 experiment to evaluate the translocation 16 of solid particles, the characteristics 17 of the particle, i.e., size and material, 18 should be considered carefully? 19 A. I agree that the size should 20 be considered very carefully. 21 Q. And did you do any 22 comparison with the size of particles 23 that are referenced in the literature 24 that you cite, to the size of particles</p>	<p style="text-align: right;">Page 429</p> <p>1 of the animal studies certainly 2 fall within the range that I just 3 gave you. 4 BY MR. HEGARTY: 5 Q. Well, a number of the animal 6 studies used nanoparticles, correct? 7 A. They used .1 micron, but 8 they also used larger particles. 9 Q. Is it your testimony that 10 there are nanoparticles of talc in 11 Johnson's Baby Powder? 12 A. If a particle -- a particle 13 is considered an ultra fine particle if 14 it's .1 micron or less. 15 Q. But my question is as to 16 nanoparticles. Are there nanoparticles 17 in Johnson's Baby Powder? 18 A. Not that your literature 19 showed. But ultra fines are also -- can 20 be called nanoparticles because they go 21 as low as .1. 22 Q. If you look over on Page 14 23 of your report, you cite in the second 24 paragraph a letter from FDA to</p>

<p style="text-align: right;">Page 430</p> <p>1 Dr. Epstein, correct?</p> <p>2 A. That's correct.</p> <p>3 Q. I marked as Exhibit</p> <p>4 Number 33 a copy of that letter.</p> <p>5 (Document marked for</p> <p>6 identification as Exhibit</p> <p>7 Zelikoff-33.)</p> <p>8 BY MR. HEGARTY:</p> <p>9 Q. Is that a copy of the letter</p> <p>10 that you are referencing in that</p> <p>11 paragraph?</p> <p>12 A. If you could point me to the</p> <p>13 paragraph, please.</p> <p>14 Q. Well, it's the second --</p> <p>15 it's the second paragraph at the top of</p> <p>16 Page 14.</p> <p>17 A. Stating "further evidence</p> <p>18 for migration"?</p> <p>19 Q. Correct.</p> <p>20 A. Okay. Yes. This is the</p> <p>21 letter that I'm referring to.</p> <p>22 Q. In the same paragraph that</p> <p>23 you reference, where you make -- where</p> <p>24 you -- in the same paragraph where you</p>	<p style="text-align: right;">Page 432</p> <p>1 A. I did not.</p> <p>2 Q. Why not?</p> <p>3 A. And in terms of my report,</p> <p>4 and talking about migration, again, the</p> <p>5 ovarian cancer and cogent biological</p> <p>6 mechanism was not appropriate for that,</p> <p>7 where I cited the original statement.</p> <p>8 Q. But you cite elsewhere in</p> <p>9 your report statements and studies you</p> <p>10 contend support your opinion that there</p> <p>11 is a biologically plausible mechanism</p> <p>12 between talc and ovarian cancer, correct?</p> <p>13 A. Yes, I do.</p> <p>14 Q. This statement by FDA</p> <p>15 concerns whether there's a biologically</p> <p>16 plausible mechanism between talc and</p> <p>17 ovarian cancer, correct?</p> <p>18 A. That is -- that is what the</p> <p>19 FDA says, yes.</p> <p>20 Q. Did you cite FDA's statement</p> <p>21 about -- as to its view of whether a</p> <p>22 cogent biological mechanism exists</p> <p>23 anywhere in your report?</p> <p>24 A. I did not cite this</p>
<p style="text-align: right;">Page 431</p> <p>1 pull out the statement that you cite</p> <p>2 here, "FDA states that while there exists</p> <p>3 no direct proof of talc in ovarian</p> <p>4 carcinogenesis" --</p> <p>5 A. Genesis?</p> <p>6 Q. Genesis, carcinogenesis.</p> <p>7 It's getting late for me too.</p> <p>8 Did you cite that finding by</p> <p>9 FDA in this paragraph?</p> <p>10 A. No. What I was trying to</p> <p>11 cite was referring to migration through</p> <p>12 the upper genital tract. So citing the</p> <p>13 information on carcinogenesis would not</p> <p>14 have been appropriate in that paragraph.</p> <p>15 Q. If you turn over to Page 4</p> <p>16 of the FDA's letter. At the very bottom</p> <p>17 FDA states, "A cogent biological</p> <p>18 mechanism by which talc might lead to</p> <p>19 ovarian cancer is lacking."</p> <p>20 Do you see that?</p> <p>21 A. I do see that.</p> <p>22 Q. You do not cite that</p> <p>23 statement anywhere in your report,</p> <p>24 correct?</p>	<p style="text-align: right;">Page 433</p> <p>1 statement.</p> <p>2 Q. You cite one statement by</p> <p>3 FDA that you believe they are correct</p> <p>4 about?</p> <p>5 A. They put a lot of weight</p> <p>6 into that statement and...</p> <p>7 Q. Well, how did you weigh that</p> <p>8 statement versus the other statement that</p> <p>9 I read at the bottom of Page 4?</p> <p>10 A. Sorry, I'd like to find it.</p> <p>11 And repeat the question</p> <p>12 please.</p> <p>13 Q. How did you weigh the</p> <p>14 statements you cite about migration</p> <p>15 versus the other statement that I read at</p> <p>16 the bottom of Page 4 about a cogent</p> <p>17 biologic mechanism?</p> <p>18 A. In terms of the migration,</p> <p>19 this is something that not only has been</p> <p>20 found by the FDA and -- and is being</p> <p>21 reiterated as a result of numerous</p> <p>22 studies, this, Number 4, a cogent</p> <p>23 biological mechanism by which talc led to</p> <p>24 ovarian cancer is lacking is the FDA's</p>

<p style="text-align: right;">Page 434</p> <p>1 opinion in 19 -- in 2014, and I did not 2 know at all how they came to that 3 conclusion. 4 So in terms of migration, 5 that's been ferreted out and it's well 6 known in the literature for migration of 7 particles. But the -- their opinion, the 8 FDA's opinion on this, I could not 9 substantiate in terms of what they were 10 basing that conclusion on. 11 Q. What methodology did you use 12 to determine which of the statements by 13 FDA in this letter you believed are 14 correct and which you believed are not 15 correct? 16 MS. O'DELL: Object to the 17 form. 18 THE WITNESS: Well, if it 19 was a common finding such as that 20 which particles can migrate which 21 has been shown since late 1990s, 22 versus information that is given 23 in this report and is the basis -- 24 and is what the FDA is opining on,</p>	<p style="text-align: right;">Page 436</p> <p>1 scrutiny. I think that for what they 2 did, they did a good study. 3 Q. If you look at Page 3 of the 4 FDA letter. 5 A. Okay. 6 Q. At the bottom, do you see 7 they comment on the very NTP study -- 8 A. Yes. 9 Q. -- that you just mentioned, 10 right? 11 MS. O'DELL: Which page are 12 you on? 13 MR. HEGARTY: Page 3. 14 THE WITNESS: There were a 15 number -- 16 BY MR. HEGARTY: 17 Q. I'm not -- I'm haven't asked 18 a question. 19 A. Oh, I'm sorry. 20 Q. My question was simply, do 21 you see where they comment on that NTP 22 study? 23 A. I see that, yes. 24 Q. Do you cite anywhere in your</p>
<p style="text-align: right;">Page 435</p> <p>1 however, I don't know what the -- 2 what the literature is that they 3 reached in that conclusion. 4 BY MR. HEGARTY: 5 Q. IARC includes a citation in 6 its 2010 monograph saying essentially 7 that the evidence of migration to the 8 ovaries is weak. Do you recall reading 9 that? 10 A. I do not recall reading 11 that. I've reviewed the IARC paper, but 12 I -- I do not recall. And I could look 13 at it and tell you what I thought. 14 Q. You made reference earlier 15 in the deposition to the 1992 NTP study, 16 correct? 17 A. Yes. 18 Q. Do you find that to be a 19 well-done study? 20 A. For what it was, I do find 21 it to be a well-done study. I've worked 22 with the NTP. I've served as an advisory 23 board member. And I think that the work 24 they do are -- is with rigor and</p>	<p style="text-align: right;">Page 437</p> <p>1 report FDA's commentary on the NTP study? 2 A. I can find it in my report. 3 I did comment on some of the other that 4 there's been some controversy by 5 Dr. Warheit and Dr. Goodman. They had 6 some pushback on this. I think I 7 commented on that, but I'd like to find 8 the page where I said that. 9 Q. You agree that you didn't 10 cite to FDA's commentary about the NTP 11 study in its February 14, 2014, letter? 12 A. Not -- not that I recall, 13 no. But as I said, I did comment on 14 other -- their -- the FDA's comments are 15 very similar to those made by other 16 scientists. 17 Q. You say the FDA's comments 18 are very similar to those made by other 19 scientists. You are talking about the 20 comments on Page 3? 21 A. I am. And I'm talking about 22 the comments made by Dr. Jay Goodman and 23 Dr. David Warheit that pushed back on the 24 studies by the NTP and the conclusion.</p>

<p style="text-align: right;">Page 438</p> <p>1 Q. For purposes of your 2 analysis in this case, did you review all 3 the studies on talc miners and millers? 4 A. No, I did not. 5 Q. For purposes -- 6 A. I am not an epidemiologist. 7 Q. For purposes of your 8 analysis in this case, did you look at 9 all the studies looking at talc -- 10 looking at long-term effects of talc 11 pleurodesis? 12 MS. O'DELL: Object to the 13 form. 14 THE WITNESS: It was -- it 15 was not my question to look at -- 16 only to bring the pulmonary 17 aspects in in manners that relate 18 to ovarian effects and 19 inflammation and plausibility. 20 So, no, I did not. I 21 reviewed several studies on 22 pleurodesis, in terms of 23 understanding it, why talcum 24 powder is used, and the effect of</p>	<p style="text-align: right;">Page 440</p> <p>1 So when you're looking at 2 toxicology, it's not just the 3 concentration that you use. It's 4 also the length and duration and 5 frequency of the use and their 6 cumulative effects. 7 BY MR. HEGARTY: 8 Q. Is it your opinion that a 9 single particle of talc is sufficient for 10 biologic plausibility? 11 MS. O'DELL: Objection to 12 form. 13 THE WITNESS: I'm pretty 14 sure I answered that question 15 before. But I will -- again, 16 talcum powder is known to produce 17 inflammation, and inflammation is 18 known to be a biological mechanism 19 for cancer. 20 BY MR. HEGARTY: 21 Q. My question is, is a single 22 particle of talc in vivo sufficient for 23 your biologic plausibility opinion in 24 this case?</p>
<p style="text-align: right;">Page 439</p> <p>1 talcum powder on pleurodesis. 2 BY MR. HEGARTY: 3 Q. What is the volume of talc 4 that gets introduced in vivo with a 5 single application to the perineum? 6 MS. O'DELL: In pleurodesis? 7 THE WITNESS: For 8 pleurodesis? 9 BY MR. HEGARTY: 10 Q. No, just in women in 11 applying -- strike that. 12 MS. O'DELL: I'm sorry. 13 BY MR. HEGARTY: 14 Q. What is the volume of talc 15 that gets introduced in vivo with a 16 single application of talc to the 17 perineum? 18 MS. O'DELL: Objection to 19 form. 20 THE WITNESS: I do not know 21 the concentration. It depends on 22 the person and how they're using 23 it. It also depends on the 24 frequency that they are using it.</p>	<p style="text-align: right;">Page 441</p> <p>1 A. If it produces inflammation, 2 it could be used that way. As a matter 3 of relevancy, I don't think that there's 4 anyone who produces -- who uses a single 5 molecule. But in answer to your 6 question, if that single talc -- talcum 7 powder product produced inflammation, 8 then yes, it could -- it could be related 9 to biological plausibility. 10 Q. Can you cite any published 11 authority that supports that opinion? 12 A. That shows me that one 13 particle could produce inflammation? 14 Q. That could lead to cancer. 15 A. That could lead to cancer. 16 I cannot show you. It's not that I don't 17 know if it's there or not there. I just, 18 to my knowledge, I am not aware. 19 MR. HEGARTY: I'm going to 20 let Mr. Ferguson ask you some 21 questions for a little bit. Then 22 I will come back and finish up. 23 THE WITNESS: Okay. Thank 24 you.</p>

<p style="text-align: right;">Page 442</p> <p>1 THE VIDEOGRAPHER: The time 2 is 6:00 p.m. Off the record. 3 (Short break.) 4 THE VIDEOGRAPHER: The time 5 is 6:25 p.m. Back on the record. 6 - - - 7 EXAMINATION 8 - - - 9 BY MR. FERGUSON: 10 Q. Hello, Dr. Zelikoff. 11 A. Hello. 12 Q. How are you? 13 A. Good, thank you. 14 Q. My name is Ken Ferguson, and 15 I represent Imerys, one of the parties to 16 this litigation. Do you understand that? 17 A. I understand what you said, 18 yes. 19 Q. Okay. And I'm going to have 20 some questions for you, which I'm going 21 to maybe try to go through pretty 22 quickly. But just stop me if I speed up 23 too much. I'm told that I talk slowly. 24 So maybe I won't be speeding up too much.</p>	<p style="text-align: right;">Page 444</p> <p>1 Q. Have you ever been elected 2 to membership in any of the national 3 academies, for example the National 4 Academy of Science? 5 A. I've not been elected as a 6 member, but I have served on the advisory 7 body numerous times. 8 Q. Okay. But you haven't been 9 elected to membership; is that right? 10 A. No, that is correct. 11 Q. Dr. Zelikoff, have you 12 communicated with any regulatory bodies 13 of any country regarding the issue of 14 talc and ovarian cancer that we've been 15 discussing today? 16 A. I have not. 17 Q. Have you communicated with 18 any scientific journals or publications 19 regarding talc and ovarian cancer? 20 A. I have not. 21 Q. So, can you turn to your 22 report, which is Exhibit Number 2. 23 A. I have it. 24 Q. Okay. Can you look at the</p>
<p style="text-align: right;">Page 443</p> <p>1 So first of all, let me just 2 go back briefly to your background and 3 qualifications. 4 A. Okay. 5 Q. Just briefly, do you 6 currently have a laboratory? 7 A. I do have a laboratory. 8 Q. And how many personnel do 9 you have employed in the laboratory? 10 A. Today? 11 Q. Yes, ma'am. 12 A. Today I have no one 13 employed, but three graduate students. 14 Q. And where does the funding 15 come from to support that laboratory? 16 A. It comes from the NIEHS, 17 National Institute of Environmental 18 Health Sciences from a center grant. And 19 that is the main source at this moment. 20 Q. Are you the principal 21 investigator of any extramural or 22 intramural funding at the current time? 23 A. I have -- as of today, I'm 24 not.</p>	<p style="text-align: right;">Page 445</p> <p>1 top of Page 3, please. 2 A. Yes, sir. 3 Q. And in the first full 4 paragraph on that page, it says, "My 5 opinions below are based upon my 6 experience as a toxicologist and research 7 scientist and have been reached through 8 employing the same scientific methodology 9 and rigor that I employ in my academic 10 research and professional duties." 11 Correct? 12 A. Yes, sir, I see that. 13 Q. And is that true? 14 A. That is true. 15 Q. And in your professional 16 duties and academic research, do you 17 customarily rely on peer-reviewed 18 publications in the scientific literature 19 for your research? 20 A. I do -- peer reviews, I rely 21 on. Abstracts come into play. 22 Documents. Whatever is needed, I will 23 use and cite in my publications. 24 Q. Do you customarily rely on</p>

<p style="text-align: right;">Page 446</p> <p>1 non-peer-reviewed research that is paid 2 for by a party that has a direct 3 financial interest in the outcome of the 4 study? 5 MS. O'DELL: Object to the 6 form. 7 THE WITNESS: I go by the 8 science. I don't look at the 9 funding. Many scientists do. But 10 I think if the science is sound, I 11 look at the science -- I go by the 12 science. 13 BY MR. FERGUSON: 14 Q. Look at -- look at Page 8, 15 please. 16 A. Yes, sir. 17 Q. There in the first full 18 paragraph, you talk about recent TEM 19 testing on historic samples. 20 Do you see that sentence? 21 A. Recent TEM testing on 22 historic samples, yes. 23 Q. And you cite Longo and 24 Rigler from 2018, correct?</p>	<p style="text-align: right;">Page 448</p> <p>1 testing from the company? 2 BY MR. FERGUSON: 3 Q. And my question was, can you 4 cite any scientific articles that you've 5 authored in which you cited an 6 unpublished paper authored by an expert 7 witness who is being paid in the 8 litigation on the very topic that you're 9 writing on? 10 A. I have not had that 11 opportunity so the answer is no. 12 Q. So, you've never done that 13 in your academic writings, correct? 14 A. If you mean that -- by that, 15 that I have never cited an unpublished 16 paper authored by an expert witness? 17 Q. Yes, ma'am. 18 A. I have not done -- I have 19 not had the opportunity to do that. My 20 publications are primarily, if not 21 solely, based either on reviews or -- or 22 results that have emerged from my own 23 laboratory or a colleague's laboratory. 24 I've not had that</p>
<p style="text-align: right;">Page 447</p> <p>1 A. Mm-hmm-hmm, yes. 2 Q. Okay. And are you aware 3 that Longo and Rigler are paid expert 4 witnesses who were hired by plaintiffs' 5 counsel to testify in talc litigation, 6 including this matter you're working on? 7 A. I understand -- I understand 8 today that they are plaintiffs' 9 witnesses, experts. 10 Q. Can you cite any scientific 11 articles that you've authored in the past 12 in which you cited an unpublished paper 13 that was authored by expert witnesses 14 hired by a party in litigation on the 15 very topic that you're writing on? 16 MS. O'DELL: Objection to 17 form. 18 THE WITNESS: I relied 19 primarily on Longo. But it is, as 20 I said, or as I will say, it's a 21 Johnson & Johnson product that 22 they are testing, so in my 23 opinion, who better to know what's 24 there than someone who did the</p>	<p style="text-align: right;">Page 449</p> <p>1 opportunity. So the answer is no. 2 Q. If you look at Page 7. 3 A. Of the report? 4 Q. Of -- of your report. Yes 5 please. 6 On Page 7 you say, "In 2004, 7 a television station reported that 8 Johnson's Baby Powder had been analyzed 9 and found anthophyllite asbestos at 10 0.2 percent," correct? 11 A. I see that. That's in the 12 last paragraph. The second sentence: In 13 2004, a television station reported 14 Johnson's Baby Powder had been analyzed 15 and found anthophyllite asbestos at 16 0.2 percent, yes. 17 Q. In your previous academic 18 research, have you ever cited to stories 19 run on local television stations? 20 A. I have. 21 Q. And is that something that 22 you think shows scientific rigor? 23 MS. O'DELL: Objection to 24 form.</p>

<p style="text-align: right;">Page 450</p> <p>1 THE WITNESS: It depends on 2 the scientific paper. And it -- 3 it depends on the source of the 4 media. 5 BY MR. FERGUSON: 6 Q. If we go to Pages 6 -- 7 A. If -- if I may add to that, 8 my recollection is that that television 9 station data was given to Johnson & 10 Johnson and it was not -- I did not cite 11 television station itself, but the -- the 12 document that was turned over to Johnson 13 & Johnson. 14 Q. If you go to Page 6 of 15 your -- 16 A. Page what, I'm sorry? 17 Q. 6. 18 A. 6? 19 Q. So on Pages 6 to 8 you cite 20 documents or other sources that you claim 21 show the presence of asbestos in talc 22 powder, correct? You -- 23 A. Pages 6 to 8? 24 Q. Yeah. Why don't you go to</p>	<p style="text-align: right;">Page 452</p> <p>1 BY MR. FERGUSON: 2 Q. And that's in your report, 3 correct? 4 A. On Page 7 at the top. 5 Q. Then you also cited 6 Dr. Blount's paper that you and 7 Mr. Hegarty talked about, correct? 8 A. I'm sorry, can you give me a 9 location? 10 Q. Sure. It's the second 11 paragraph on Page 7. 12 A. Van Gosen? 13 Q. No, the second full 14 paragraph, cosmetic and pharmaceutical 15 talc products, et cetera -- 16 A. Yes, deposition of Alice 17 Blount. Yes. 18 Q. Correct. 19 A. Sorry to interrupt. 20 Q. And Dr. Blount's paper was 21 some 30 or so years ago, correct? 22 A. 1991. 23 Q. And -- and I won't go 24 through this in detail, but Mr. Hegarty</p>
<p style="text-align: right;">Page 451</p> <p>1 the top of 7. Let me go to it 2 specifically. 3 One of the things you cite 4 to is Paoletti in 1984? 5 A. Yes, sir. 6 Q. Okay. And the Paoletti 7 study was completed -- I don't know if I 8 can do my math very well, but is that 9 36 years ago? 10 A. 36, yes. 11 Q. And you notice they have 12 assessed, according to your own report, 13 contamination in industrial and cosmetic 14 talcs, correct? 15 A. 9 of the 24 pharmaceutical 16 and cosmetic grade talcs contain 17 tremolite fibers. 18 Q. And they are from the 19 Italian market, correct? 20 A. From the Italian market. 21 MS. O'DELL: Objection to 22 form. 23 THE WITNESS: And the 24 European pharmacopeia.</p>	<p style="text-align: right;">Page 453</p> <p>1 discussed with you the fact that U.S. 2 Food and Drug Administration conducted a 3 survey of cosmetic grade raw material 4 talc and some cosmetic products 5 containing talc. And you were generally 6 aware of that, correct? 7 A. The FDA report that he -- he 8 pointed me to, yes. 9 Q. Okay. You were aware but 10 you didn't cite it, correct? 11 A. I was aware but I did not 12 cite it. 13 Q. And that came from 2010 as 14 opposed to 1984 or 1991, correct? 15 MS. O'DELL: Objection -- 16 THE WITNESS: Yes -- 17 MS. O'DELL: Excuse me. 18 Objection to form. 19 If you're going to ask a 20 specific -- about a specific date, 21 I would ask -- or a specific item 22 of that -- in that document I 23 would just ask that you show the 24 witness.</p>

<p style="text-align: right;">Page 454</p> <p>1 BY MR. FERGUSON:</p> <p>2 Q. Do you -- do you recall when</p> <p>3 that survey was from?</p> <p>4 A. The FDA was 2014. I don't</p> <p>5 recall a specific.</p> <p>6 Q. Well, okay. Counsel's</p> <p>7 suggested it. Why don't we go ahead and</p> <p>8 mark as Exhibit 37.</p> <p>9 (Document marked for</p> <p>10 identification as Exhibit</p> <p>11 Zelikoff-37.)</p> <p>12 BY MR. FERGUSON:</p> <p>13 Q. And is this a document that</p> <p>14 you've reviewed before?</p> <p>15 A. This is a document that I</p> <p>16 have reviewed, yes.</p> <p>17 Q. Okay. If you look at Page 2</p> <p>18 at the top of the page, in the second</p> <p>19 paragraph there, it says, "The study ran</p> <p>20 from September 28, 2009, to September 27,</p> <p>21 2010," correct?</p> <p>22 A. So I'm trying to put that</p> <p>23 sentence into context. So I need to read</p> <p>24 the above sentences.</p>	<p style="text-align: right;">Page 456</p> <p>1 Luzenac America, correct?</p> <p>2 A. Correct. On the left side.</p> <p>3 Q. On the left side. And on</p> <p>4 the right side there are two columns that</p> <p>5 say percentage asbestos by PLM and</p> <p>6 percentage asbestos by TEM, correct?</p> <p>7 A. I see that.</p> <p>8 Q. And each of those says NAD,</p> <p>9 correct?</p> <p>10 A. They say NAD.</p> <p>11 Q. And from your review of</p> <p>12 this, do you know that NAD means no</p> <p>13 asbestos detected?</p> <p>14 A. Yes, I do. That means that</p> <p>15 the measurements that they had and the</p> <p>16 scientific -- and the sensitivities that</p> <p>17 they were using at the given time, they</p> <p>18 did not see any, is my interpretation of</p> <p>19 that.</p> <p>20 Q. According to the paper that</p> <p>21 you said, NAD means no asbestos detected,</p> <p>22 correct?</p> <p>23 A. In this study, yes, correct.</p> <p>24 Q. Let's take a look. You've</p>
<p style="text-align: right;">Page 455</p> <p>1 I assume that the study they</p> <p>2 are talking about was the contract with</p> <p>3 the AMA analytical services to conduct</p> <p>4 the laboratory survey.</p> <p>5 Is that the study that they</p> <p>6 are referring to? It's unclear.</p> <p>7 Q. And in your review of this</p> <p>8 document, did you read that there was no</p> <p>9 asbestos detected by the survey by the</p> <p>10 FDA in either the cosmetic grade raw</p> <p>11 material talc, or the finished product</p> <p>12 cosmetic products containing talc,</p> <p>13 correct?</p> <p>14 A. I'm trying to find where</p> <p>15 that was stated.</p> <p>16 Q. If you look at Page 3?</p> <p>17 A. Yes, sir.</p> <p>18 Q. See where it says at the top</p> <p>19 of the page, "Cosmetic raw material</p> <p>20 talc"?</p> <p>21 A. I see that, yes, sir.</p> <p>22 Q. Correct?</p> <p>23 Then there is a list of</p> <p>24 suppliers called Rio Tinto Minerals</p>	<p style="text-align: right;">Page 457</p> <p>1 cited to IARC several times during</p> <p>2 your -- in your report, correct?</p> <p>3 A. Yes, I did.</p> <p>4 Q. And let's look at the IARC</p> <p>5 monograph 100 C, which was published in</p> <p>6 2012 that I've marked as Exhibit 36.</p> <p>7 (Document marked for</p> <p>8 identification as Exhibit</p> <p>9 Zelikoff-36.)</p> <p>10 THE WITNESS: Entitled</p> <p>11 Arsenic Metals, Fibrous and Dusts?</p> <p>12 BY MR. FERGUSON:</p> <p>13 Q. Correct.</p> <p>14 And if you -- I've provided</p> <p>15 you a page there, correct?</p> <p>16 A. You've provided me with</p> <p>17 three pages.</p> <p>18 Q. Okay. And was that</p> <p>19 Page 225?</p> <p>20 A. 225 starts 1.5 human</p> <p>21 exposure.</p> <p>22 Q. Okay. If you look at the</p> <p>23 top of 225. Do you have that page?</p> <p>24 A. Yes, sir.</p>

<p style="text-align: right;">Page 458</p> <p>1 Q. In an exposure it says, 2 "Inhalation and ingestion are the primary 3 routes of exposure to asbestos," correct? 4 MS. O'DELL: Objection to 5 form. 6 BY MR. FERGUSON: 7 Q. The very first sentence. 8 A. Mm-hmm-hmm. I cannot attest 9 to ingestion, but certainly inhalation is 10 a primary. 11 Q. But you'd agree that -- that 12 this is what IARC said, correct? 13 A. I agree that this is what's 14 in IARC, yes, 2012. 15 Q. And then there's another 16 section called exposure of the general 17 population, correct? 18 A. Yes, sir. 19 Q. And in the second paragraph 20 under that, do you see that paragraph 21 starts in studies of asbestos 22 concentrations? 23 A. I do. 24 Q. Okay. And -- and let's --</p>	<p style="text-align: right;">Page 460</p> <p>1 A. That's what's here, yes. 2 Q. Okay. So certainly based on 3 what IARC has said, a person could inhale 4 or ingest one or more asbestos fibers 5 from the air that they breathe, correct? 6 MS. O'DELL: Objection to 7 form. 8 THE WITNESS: Based on the 9 measurements, I can't really tell 10 where they took these, where they 11 took the measurements or how they 12 measured them, from this Page 225, 13 but based on what they are saying 14 here, they have measured in 15 outdoor air and rural locations, 16 10 fibers per cubic meter, yes. 17 As I said, if you look down 18 in that paragraph it also 19 indicates that asbestos has been 20 measured in the air in a disaster 21 such as the World Trade Center, in 22 higher concentrations by 23 Dr. Longo. 24 BY MR. FERGUSON:</p>
<p style="text-align: right;">Page 459</p> <p>1 let's read it and see if it -- you and I 2 agree on what it says. 3 "In studies of asbestos 4 concentrations in outdoor air, chrysotile 5 is the predominant fiber detected. Low 6 levels of asbestos have been measured in 7 outdoor air in rural locations; typical 8 concentration, 10 fibers per cubic meter. 9 Typical concentrations are about tenfold 10 higher in urban locations and about 1,000 11 times in close proximity to industrial 12 sources of exposure, e.g., asbestos mine 13 or factory demolition site, or improperly 14 protected asbestos-containing waste 15 site," correct? 16 A. That's what's written here, 17 yes. 18 Q. Okay. And if you go down to 19 the first sentence of the next paragraph, 20 it says, "In indoor air, for example in 21 homes, schools and other buildings, 22 measured concentrations of asbestos are 23 in the range of 30 to 6,000 fibers per 24 cubic meter," correct?</p>	<p style="text-align: right;">Page 461</p> <p>1 Q. And then if you look at 2 Page 229. Are you with me? 3 A. Yes, I am. 4 Q. Under B, dietary exposure. 5 A. Yes. 6 Q. It says in the first 7 sentence under that paragraph heading, 8 "The general population can be exposed to 9 asbestos in drinking water," correct? 10 A. It can happen under certain 11 conditions, yes. It says, "The general 12 population can be exposed to asbestos in 13 drinking water." 14 Q. And then below it says about 15 nine lines down, "In the U.S.A., the 16 concentration of asbestos in most 17 drinking water supplies is less than one 18 fiber per milliliter even in areas with 19 asbestos deposits or with asbestos cement 20 water supply pipes." Correct? 21 A. That's what it says here. 22 Q. And then it says, "However, 23 in some locations the concentration in 24 water may be extremely high containing 10</p>

<p style="text-align: right;">Page 462</p> <p>1 to 300 million fibers per liter or even 2 higher." Correct? 3 MS. O'DELL: Objection to 4 form. 5 THE WITNESS: That's what it 6 says here. 7 BY MR. FERGUSON: 8 Q. So -- 9 A. But it's talking about -- 10 it's talking about specific locations and 11 it's also saying "can." This is not a 12 normal situation. Normal -- this is a 13 contaminated situation. 14 Q. But as IARC said, in the 15 first line we talked about, inhalation 16 and ingestion can be routes of exposure 17 to asbestos for the general population, 18 correct? 19 A. It can be. Can being the 20 keyword. 21 Q. I've got some more questions 22 that I could ask. But I'm going to pass 23 it back to Mr. Hegarty. 24 THE WITNESS: Hello again.</p>	<p style="text-align: right;">Page 464</p> <p>1 (Whereupon, a discussion was 2 held off the record.) 3 THE VIDEOGRAPHER: The time 4 is 6:46 p.m. Back on the record. 5 - - - 6 EXAMINATION 7 - - - 8 BY MR. HEGARTY: 9 Q. Doctor, you have done a 10 number of studies looking at inhalation 11 of particles in animal species primarily, 12 correct? 13 A. In animal species primarily, 14 but also I have done studies in cell 15 culture, yes. 16 Q. In any of the studies where 17 you have looked at inhalation of 18 particles in animals, have you reported 19 finding those particles in the ovaries? 20 A. I did not look in the 21 ovaries. 22 Q. So have you ever evaluated 23 the ovaries in any study that you have 24 done?</p>
<p style="text-align: right;">Page 463</p> <p>1 MR. HEGARTY: Hello again. 2 MS. O'DELL: So are you 3 finished with your questions? 4 MR. FERGUSON: I have other 5 questions that I could ask. But 6 I'm trying to share the limited 7 time that we have. 8 MS. O'DELL: I understand. 9 I'm just trying -- typically we 10 don't go back and forth between 11 the parties. The plaintiffs' side 12 has had time to ask questions. So 13 I guess I'm just trying to figure 14 out what y'all are doing. 15 MR. HEGARTY: Let's go off 16 the record real quick and have a 17 discussion. Because what we 18 planned to do, I took the time 19 that Ken was using to organize my 20 notes and to finish up the 21 remaining time. 22 Go off the record. 23 THE VIDEOGRAPHER: The time 24 is 6:45 p.m. Off the record.</p>	<p style="text-align: right;">Page 465</p> <p>1 A. I have evaluated -- in the 2 cadmium particle studies, we looked for 3 the soluble ions, that's what we 4 measured, using atomic absorption and ICT 5 mass spec. And we did find cadmium -- 6 sorry. Sorry. We did find soluble 7 cadmium ions in the -- in the tissue -- 8 in the ovaries. 9 Q. Of what animal? 10 A. Mice. 11 Q. So there's nothing unique 12 with regard to talc in your opinion with 13 regard to its ability to transport within 14 the body, correct? 15 MS. O'DELL: Object to the 16 form. 17 THE WITNESS: Talc is a 18 fiber and will transport as a 19 fiber. It's also hydrophilic so 20 it will require some time for the 21 other products within the talc 22 molecule to be released. I am not 23 sure if I answered your question. 24 BY MR. HEGARTY:</p>

<p style="text-align: right;">Page 466</p> <p>1 Q. What about platy talc? Will 2 platy talc travel in the body as cadmium 3 would travel? 4 A. Cadmium is a -- has traveled 5 as a soluble ion. So platy talc -- 6 neither platy talc nor asbestos will 7 travel as a soluble ion. They are 8 fibers. 9 Q. Have you done -- 10 A. They are -- I'm sorry, platy 11 talc is a crystal with different forms. 12 But my understanding is that platy talc 13 can fracture and also form fragments and 14 they could travel, given their size. 15 Q. Could they travel as cadmium 16 has traveled in your studies, if that 17 happens? 18 A. No, in -- in my studies we 19 did not measure -- we did not look for 20 the presence of the particle -- of the 21 nanoparticle in the tissues. We measured 22 for the metal in those tissues. 23 So we are of the opinion 24 that it was the soluble ion that was</p>	<p style="text-align: right;">Page 468</p> <p>1 to reach -- it can reach the deep lung, 2 if it's five micrometers or smaller. 3 And -- 4 Q. Go ahead. 5 A. And in that case since it's 6 not disposed of through the mucociliary 7 escalator, then it is in the other parts 8 of the lung and it can reach the 9 capillaries. And once it gets into the 10 bloodstream, it can be transported. 11 Certain particles have predilections for 12 where they go. 13 Q. When you say it can be 14 transported, does that include to the 15 ovaries? 16 A. Are you asking specifically 17 about talc or particles in general? 18 Q. Particles in general that 19 meet the size standards that you just 20 referenced of getting into the deep lung? 21 A. Mm-hmm-hmm. There's no 22 reason not to believe that it couldn't 23 get into the ovaries. 24 Q. Did you examine, for</p>
<p style="text-align: right;">Page 467</p> <p>1 released, and in this case, I know of no 2 studies off the top of my head that 3 measured how much of the other components 4 were released. 5 Q. Can any particle that's 6 inhaled reach the ovary? 7 A. If it -- if it meets certain 8 size constituents. There's no reason why 9 a particle could not reach the ovary or 10 the kidney or the liver or -- under 11 proper circumstances. 12 Q. Is there a certain size 13 limitation? 14 A. Well, something that's 15 inhaled, is that what you're talking 16 about? 17 Q. Yes. 18 A. Something that's inhaled, if 19 it's 10 micrometers or greater, it's 20 going to be caught in the upper airways 21 and probably dismissed through the 22 mucociliary escalator. If it's of a 23 smaller nature, then depending on where 24 the impaction is for the lung, it's going</p>	<p style="text-align: right;">Page 469</p> <p>1 purposes of your biological plausibility 2 opinion, all the studies looking at 3 NSAIDs and use of aspirin in women with 4 ovarian cancer? 5 A. I looked at several studies. 6 I'm sure I -- 7 (Document marked for 8 identification as Exhibit 9 Zelikoff-38.) 10 BY MR. HEGARTY: 11 Q. I'm going to show you what I 12 marked as Exhibit 38, which is a study 13 that you cited by Wu 2009. 14 A. Actually, it's Merritt. 15 Q. I'm sorry. It's Merritt 16 2008, correct? 17 A. Yes. And let me find it in 18 my report. 19 Q. You cite it on Page 26. 20 Above the italicized paragraph -- 21 italicized paragraph at the bottom. 22 A. I see it. "At high 23 concentrations with chronic exposure, 24 reactive oxygen species, known as ROS,</p>

<p style="text-align: right;">Page 470</p> <p>1 can damage cellular macromolecules and 2 contribute to neoplastic transformation 3 and/or tumor growth. Other likely 4 manifestations of talc." That's the 5 paragraph that you're referring to. 6 Q. You do agree that a relevant 7 body of literature is whether NSAIDs or 8 aspirin have an effect on ovarian cancer 9 risk, if you're considering inflammation 10 as a biologically plausibility mechanism. 11 A. NSAIDs being an -- one type 12 of anti-inflammatory, it could reduce 13 oxidative stress, yes, to different 14 degrees. 15 Q. If you look at the abstract 16 on the first page of the Merritt paper. 17 A. Yes. 18 Q. At the very end, they say, 19 "We conclude that on balance chronic 20 inflammation does not play a major role 21 in the development of ovarian cancer." 22 Do you see where I'm 23 reading? 24 A. I'm seeing the last</p>	<p style="text-align: right;">Page 472</p> <p>1 on Page 21 of your report? 2 A. Can you direct me to it? 3 Oh, I see it. Second paragraph. "Wu, et 4 al, 2009, performed a study to determine 5 the role of talc in the development of 6 ovarian cancer considering the history of 7 endometriosis." 8 Q. If you look at the abstract 9 of the Wu paper, about two-thirds of the 10 way down, it reads, "Contrary to the 11 hypothesis." 12 Do you see that start of the 13 sentence? 14 A. I do. 15 Q. "Contrary to the hypothesis 16 that risk of ovarian cancer may be 17 reduced by use of NSAIDs, risk increased 18 with increasing the frequency in years of 19 NSAID use," citing the relative risk, the 20 confidence intervals. "This was 21 consistent across types of incident." 22 Do you see where I'm 23 reading? 24 A. I do see where you're</p>
<p style="text-align: right;">Page 471</p> <p>1 sentence, yes. 2 Q. Do you agree with that 3 statement in general? 4 A. I do not agree with that 5 statement. That's -- my biological 6 plausibility is associated with the 7 oxidative stress and inflammation. Also 8 this paper was written in 2008. 9 Q. Did you cite that finding 10 that I just read anywhere in your report? 11 A. I cite Merritt. 12 Q. Do you cite for the reader 13 of your report the statement that I just 14 read in the abstract? 15 A. Not to my recollection. 16 (Document marked for 17 identification as Exhibit 18 Zelikoff-39.) 19 BY MR. HEGARTY: 20 Q. I'm showing you what I've 21 marked as Exhibit Number 39. That is the 22 Wu paper. 23 A. Mm-hmm-hmm. 24 Q. You cite the Wu paper over</p>	<p style="text-align: right;">Page 473</p> <p>1 reading. 2 Q. That finding is inconsistent 3 with inflammation as a mechanism by which 4 ovarian cancer can occur, correct? 5 MS. O'DELL: Object to the 6 form. 7 THE WITNESS: This -- NSAIDs 8 are known as antioxidants. And 9 yes, that's true, but there are 10 other antioxidants from other 11 papers that demonstrate that it 12 does indeed reduce inflammation. 13 BY MR. HEGARTY: 14 Q. Well, did you cite the 15 finding of the Wu paper with regard to 16 its data on NSAID use and the risk of 17 ovarian cancer? 18 A. I did have a section, to my 19 recollection, on the papers of Wu and 20 Merritt. 21 Q. Well, in the section that I 22 was referring to, in the middle of the 23 paragraph on Page 21, middle paragraph on 24 Page 21, you don't cite that study's</p>

<p style="text-align: right;">Page 474</p> <p>1 findings as to NSAIDs and risk of ovarian 2 cancer, correct? 3 A. I do not cite that 4 particular sentence, no. 5 Q. Over on Page 23, you refer 6 to the Shukla study? 7 A. Yes, sir. 8 Q. That's second to the last 9 paragraph? 10 A. "In a molecular cell study 11 by Shukla"? 12 Q. Yes. The -- strike that. 13 Gene expressions like those 14 measured in the Shukla study occur 15 everyday in everyone, correct? 16 MS. O'DELL: Objection to 17 form. 18 THE WITNESS: There are 19 changes in genes per day. But 20 I'm -- I'm not -- I do not know 21 nor do I have knowledge of whether 22 the gene for ATF3 or ATF1 is 23 changed everyday by no exposure. 24 BY MR. HEGARTY:</p>	<p style="text-align: right;">Page 476</p> <p>1 proinflammatory cytokines and oxidase, 2 yes. 3 Q. Is there any study that 4 sites the clinical significance of ATF as 5 it relates to ovarian cancer risk? 6 MS. O'DELL: Object to the 7 form. 8 THE WITNESS: No study that 9 I'm currently aware of. But there 10 are many studies that link ATF 11 upregulation to inflammation and 12 then inflammation to -- in the 13 process of carcinogenesis, both 14 progression and initiation. 15 BY MR. HEGARTY: 16 Q. If you turn over to the 17 second to the last page of your report, 18 Page 27. 19 In Paragraph 3, you say that 20 exposure to talcs -- 21 A. Excuse me, Number 3? 22 Q. I called it Paragraph 3. 23 You can call it Number 3. 24 A. It's listed as Number 3.</p>
<p style="text-align: right;">Page 475</p> <p>1 Q. But the -- the fact of gene 2 expression is not a -- strike that. 3 The fact that gene 4 expression occurs does not mean that 5 cancer will occur, correct? 6 A. No. My role is to look for 7 biological plausibility, and when you 8 have a transcription factor which is so 9 well immersed into oxidation and reactive 10 oxygen species and inflammation, and I 11 would say that changes or upregulation of 12 the -- of the ATF gene certainly is 13 linked with inflammation. 14 Q. Can you cite for me any 15 studies that have used measurements of 16 level -- of the levels of ATF3 to assess 17 ovarian cancer risk? 18 A. I cannot cite those studies 19 to you, but again, going back to 20 biological plausibility, I can tell you 21 that this gene is extremely important in 22 growth factors and proinflammatory 23 cytokines. So an upregulation is going 24 to lead to the production of</p>	<p style="text-align: right;">Page 477</p> <p>1 Q. 3. You state that "exposure 2 to talcum powder products causes an 3 inflammatory tissue reaction which may 4 result in the following," and then you 5 list -- 6 A. Elevation. 7 Q. -- a number of -- of events 8 that you label as A through F -- I'm 9 sorry, A through G carrying over to the 10 top of the next page. 11 A. I see that, thank you. 12 Q. Can you cite for me any 13 studies showing any of that activity in 14 women using talc on the perineum? 15 MS. O'DELL: Object to the 16 form. 17 THE WITNESS: If I can 18 recall the Health Canada study, I 19 think they looked at -- they also 20 included inflammatory responses 21 that are seen in some of their 22 meta-analysis. 23 BY MR. HEGARTY: 24 Q. Well, the Health Canada</p>

<p style="text-align: right;">Page 478</p> <p>1 study, the Taher study, was a 2 meta-analysis, correct? 3 A. Yes, correct. 4 Q. Can you cite for me any 5 studies reporting that -- reporting these 6 events occurring in women using talc on 7 the perineum? 8 MS. O'DELL: Object to the 9 form. 10 THE WITNESS: If you're 11 asking me if gene alterations or 12 mutations or the level of 13 apoptosis has been measured in any 14 women exposed, no, I do not recall 15 that. 16 BY MR. HEGARTY: 17 Q. Have any of the processes -- 18 A. Excuse me. If I may add. 19 But inflammatory markers have been looked 20 at in women with ovarian cancer and they 21 are elevated. 22 Q. And my question, as you'll 23 recall, is specific to talc users, 24 correct?</p>	<p style="text-align: right;">Page 480</p> <p>1 as exhibit -- Exhibits 40 through 2 48 -- I'm sorry, 47 -- the 3 notebooks that had been produced 4 for purposes of the deposition 5 here today. 6 (Documents marked for 7 identification as Exhibits 8 Zelickoff-40 through 47.) 9 BY MR. HEGARTY: 10 Q. Over on Page 23, you -- 11 A. Of my report? 12 Q. Of your report, with regard 13 to the Shukla study. 14 I'm sorry, over on Page 26. 15 You cite again the Shukla study. Do you 16 see that where -- do you see where you 17 say "nonfibrous talc at low in vitro 18 exposure concentrations caused increased 19 expression of transcription factors 20 associated with the inflammatory process 21 in a time and dose dependent manner"? 22 A. I'm sorry, I'm not clear 23 on -- 24 Q. Middle of the second full</p>
<p style="text-align: right;">Page 479</p> <p>1 MS. O'DELL: Objection to 2 form. 3 THE WITNESS: Talc -- yes, 4 talc products. 5 BY MR. HEGARTY: 6 Q. Can you -- can you cite to 7 me any studies showing elevations of any 8 of these processes in women using talc? 9 MS. O'DELL: Object to the 10 form. 11 THE WITNESS: Well, 12 neoplastic transformation and 13 proliferation is clearly seen 14 in -- obviously if there's a 15 variant answer, you've had 16 neoplastic transformation 17 proliferation. 18 BY MR. HEGARTY: 19 Q. Well, my question is 20 specific to women using talc prediagnosis 21 of ovarian cancer. 22 A. I see. No, sir. 23 MR. HEGARTY: For purposes 24 of the deposition, we want to mark</p>	<p style="text-align: right;">Page 481</p> <p>1 paragraph. 2 A. Not -- after the Mori 3 citation? 4 Q. Yes. 5 A. "Nonfibrous talc at low in 6 vitro exposure concentrations caused 7 increased expression of transcription 8 factors associated with the inflammatory 9 process in a time and dose dependent 10 manner." Yes, I see that. 11 Q. What did you mean by say -- 12 by time and dose manner? 13 A. May I see the paper? 14 (Document marked for 15 identification as Exhibit 16 Zelickoff-48.) 17 BY MR. HEGARTY: 18 Q. Marking as Exhibit 49 -- 48 19 that paper. 20 A. Thank you. 21 MR. TISI: We are at seven 22 hours by the way. 23 MS. O'DELL: We are at seven 24 hours?</p>

<p style="text-align: right;">Page 482</p> <p>1 MR. TISI: Yes, we are.</p> <p>2 MS. O'DELL: We're at seven</p> <p>3 hours, Mark.</p> <p>4 MR. HEGARTY: Okay. Are you</p> <p>5 going to instruct her not to</p> <p>6 answer that question?</p> <p>7 MS. O'DELL: Well, the</p> <p>8 federal rules limit this</p> <p>9 deposition to seven hours and --</p> <p>10 MR. HEGARTY: No, I</p> <p>11 understand, but I also remember a</p> <p>12 deposition where I think I let</p> <p>13 Chris go over about two or</p> <p>14 three minutes.</p> <p>15 MR. TISI: Yeah, but you are</p> <p>16 using a whole new exhibit.</p> <p>17 MS. O'DELL: You just marked</p> <p>18 it --</p> <p>19 MR. HEGARTY: I just want to</p> <p>20 make sure that was --</p> <p>21 MR. TISI: Are you going to</p> <p>22 suggest --</p> <p>23 MR. HEGARTY: No, I just</p> <p>24 want to know if that -- if you</p>	<p style="text-align: right;">Page 484</p> <p>1 want to let her answer or not.</p> <p>2 It's simply up to you. If you say</p> <p>3 we're done, then I will -- I'm not</p> <p>4 going to dispute it.</p> <p>5 MS. O'DELL: We are -- I</p> <p>6 will let you answer that question.</p> <p>7 But after that, we're -- we're</p> <p>8 done.</p> <p>9 MR. HEGARTY: Okay. Thank</p> <p>10 you.</p> <p>11 MS. O'DELL: Do you recall</p> <p>12 the question, Dr. Zelikoff?</p> <p>13 THE WITNESS: Yes. The</p> <p>14 question is -- what -- I'll repeat</p> <p>15 it from here.</p> <p>16 What did I mean by a time</p> <p>17 and dose dependent manner?</p> <p>18 BY MR. HEGARTY:</p> <p>19 Q. Yes.</p> <p>20 A. In the Shukla study?</p> <p>21 Q. Correct.</p> <p>22 A. Well, if we look at Figure 2</p> <p>23 concerning cell viability in the Shukla</p> <p>24 paper, Page 117.</p>
<p style="text-align: right;">Page 483</p> <p>1 want to end the deposition for me</p> <p>2 right here?</p> <p>3 MR. TISI: That was a fact</p> <p>4 witness, as you know.</p> <p>5 I leave it to Leigh. If</p> <p>6 we're going to -- if we're going</p> <p>7 to have this rule, we need to kind</p> <p>8 of be consistent with it.</p> <p>9 MR. HEGARTY: No, I'm not</p> <p>10 looking to apply another rule.</p> <p>11 Just tell me whether you'll let</p> <p>12 her answer the question or if the</p> <p>13 time -- because the time is up,</p> <p>14 that question will not be</p> <p>15 answered.</p> <p>16 MS. O'DELL: The time -- the</p> <p>17 time is up. What is your -- what</p> <p>18 was your question?</p> <p>19 MR. HEGARTY: My question</p> <p>20 was, "What do you mean where you</p> <p>21 say time and dose dependent</p> <p>22 manner." But I'm not going to</p> <p>23 insist on any applicable rule.</p> <p>24 I'll let you decide whether you</p>	<p style="text-align: right;">Page 485</p> <p>1 So we can see, I'm trying to</p> <p>2 find the exact one that I want to refer</p> <p>3 to. Figure A, one can see that in terms</p> <p>4 of the concentration and over time, that</p> <p>5 the number -- total number of viable</p> <p>6 cells were altered. And in Figure 2, 15</p> <p>7 and 75 -- no, scratch Figure 2, sorry.</p> <p>8 So on Page 118, in looking</p> <p>9 at number of genes that were</p> <p>10 significantly changed, we can see looking</p> <p>11 at the concentration -- and this is for</p> <p>12 asbestos -- there was a change in effect</p> <p>13 in asbestos. If one looks at -- I think</p> <p>14 that's it. That's what I meant.</p> <p>15 MR. HEGARTY: Okay. Thank</p> <p>16 you.</p> <p>17 MS. O'DELL: Off the record.</p> <p>18 THE VIDEOGRAPHER: The time</p> <p>19 is 7:07 p.m. Off the record.</p> <p>20 (Short break.)</p> <p>21 THE VIDEOGRAPHER: We are</p> <p>22 back on the record. The time is</p> <p>23 7:30 p.m.</p> <p>24 - - -</p>

<p style="text-align: right;">Page 486</p> <p>1 EXAMINATION</p> <p>2 - - -</p> <p>3 BY MS. O'DELL:</p> <p>4 Q. Dr. Zelickoff, I have a few</p> <p>5 follow-up questions for you.</p> <p>6 Prior to your involvement in</p> <p>7 litigation, this litigation, did you hold</p> <p>8 the opinion that inflammation causes</p> <p>9 cancer?</p> <p>10 MR. HEGARTY: Objection to</p> <p>11 form.</p> <p>12 THE WITNESS: Yes. I held</p> <p>13 the opinion for a very long time</p> <p>14 that inflammation causes cancer.</p> <p>15 BY MS. O'DELL:</p> <p>16 Q. And in terms of your</p> <p>17 knowledge and opinion prior to your</p> <p>18 involvement in the litigation, did you --</p> <p>19 did you have an opinion regarding the</p> <p>20 role of oxidative stress in the</p> <p>21 development of cancer?</p> <p>22 A. Yes, I did. My opinion was</p> <p>23 that oxidative stress was closely</p> <p>24 involved with the causation of cancer.</p>	<p style="text-align: right;">Page 488</p> <p>1 A. I relied on his report, yes.</p> <p>2 Q. And did Dr. Crowley conclude</p> <p>3 that the chemicals involved in the</p> <p>4 fragrances for both Johnson & Johnson's</p> <p>5 Baby Powder and Shower to Shower may</p> <p>6 contribute to the inflammatory response,</p> <p>7 toxicity and potential carcinogenicity of</p> <p>8 Johnson & Johnson's talcum powder</p> <p>9 products?</p> <p>10 MR. HEGARTY: Objection to</p> <p>11 form.</p> <p>12 THE WITNESS: Yes. I concur</p> <p>13 with that whole opinion.</p> <p>14 BY MS. O'DELL:</p> <p>15 Q. And in fact, that's the</p> <p>16 specific opinion he included in his</p> <p>17 report that you relied on?</p> <p>18 A. Yes, that's correct.</p> <p>19 MR. HEGARTY: Objection to</p> <p>20 form.</p> <p>21 BY MS. O'DELL:</p> <p>22 Q. And so if another expert was</p> <p>23 also relying on Dr. Crowley's analysis,</p> <p>24 it wouldn't be surprising that the same</p>
<p style="text-align: right;">Page 487</p> <p>1 Q. So to the degree that your</p> <p>2 work in this case addressed new</p> <p>3 considerations, were those considerations</p> <p>4 primarily focused on talc and its ability</p> <p>5 to cause inflammation and oxidative</p> <p>6 stress?</p> <p>7 MR. HEGARTY: Objection to</p> <p>8 form.</p> <p>9 THE WITNESS: That is</p> <p>10 correct.</p> <p>11 BY MS. O'DELL:</p> <p>12 Q. Can you -- if I could ask</p> <p>13 you to take your report. I think it's</p> <p>14 right to your left. I'm going to ask</p> <p>15 you -- if you'll turn to Page 12. Do you</p> <p>16 see that? The subsection involving</p> <p>17 fragrance, fragrance chemicals?</p> <p>18 A. Yeah. C, fragrances.</p> <p>19 Q. And did you rely on</p> <p>20 Dr. Crowley's report and his review of</p> <p>21 the relevant literature and other</p> <p>22 information regarding the chemicals that</p> <p>23 are included in the fragrance for Baby</p> <p>24 Powder and Shower to Shower?</p>	<p style="text-align: right;">Page 489</p> <p>1 wording was used?</p> <p>2 MR. HEGARTY: Objection to</p> <p>3 form.</p> <p>4 THE WITNESS: Absolutely</p> <p>5 not.</p> <p>6 BY MS. O'DELL:</p> <p>7 Q. Let me ask you other</p> <p>8 questions about the general principles in</p> <p>9 your report. I think you testified, you</p> <p>10 were asked a number of questions about</p> <p>11 general principals. And in your</p> <p>12 judgment, is it generally accepted to --</p> <p>13 to use common phrasing for general</p> <p>14 principles in scientific publications?</p> <p>15 A. Yes.</p> <p>16 MR. HEGARTY: Objection to</p> <p>17 form.</p> <p>18 THE WITNESS: I answered</p> <p>19 that question before, and yes.</p> <p>20 Common, well-publicized,</p> <p>21 well-established concepts, yes.</p> <p>22 BY MS. O'DELL:</p> <p>23 Q. You were asked during the</p> <p>24 early part of the day certain questions</p>

<p style="text-align: right;">Page 490</p> <p>1 about whether you were an expert in areas 2 such as talc and inflammation? 3 A. Yes. 4 Q. And I think if you recall 5 the response you answered you were not 6 classified as an expert. What did you 7 mean by that? 8 MR. HEGARTY: Objection to 9 form. 10 THE WITNESS: What I meant 11 was in terms of legal, whether -- 12 one of the questions that arose 13 was, in the past, have I been 14 listed as an expert in other 15 cases. And so I followed that 16 line of thought and thought that 17 we were still talking about 18 litigation and formal declaration 19 as an expert in that area. 20 BY MS. O'DELL: 21 Q. Are you an expert in the 22 toxicological effects of minerals on 23 the -- on humans? 24 MR. HEGARTY: Objection to</p>	<p style="text-align: right;">Page 492</p> <p>1 A. My numerous publications in 2 that area of metal toxicology that I've 3 been doing for many, many, many years. 4 Q. And in addition to your 5 training, experience, do you also make 6 those statements based on your review of 7 the available scientific and medical 8 literature? 9 A. In regards to metals? 10 Q. In all the environmental 11 exposures we've just discussed? 12 A. Yes. I rely on 13 literature -- 14 Q. You were asked questions -- 15 A. -- as well as my own 16 scientific research. 17 Q. Excuse me. I didn't mean to 18 cut you off, Doctor. 19 You were asked questions 20 about whether there were any studies or 21 evidence that you relied on involving 22 Johnson's Baby Powder. 23 Do you recall that? 24 A. I do recall that question,</p>
<p style="text-align: right;">Page 491</p> <p>1 form. 2 THE WITNESS: I'm expert in 3 toxicology of environmental 4 chemicals, including mixtures, 5 including fibers, including 6 particles, including talc. 7 BY MS. O'DELL: 8 Q. And would that -- would that 9 also include -- when you said fibers, 10 would that also include asbestos and 11 fibrous talc? 12 MR. HEGARTY: Objection to 13 form. 14 THE WITNESS: Yes. 15 BY MS. O'DELL: 16 Q. Are you an expert in the 17 toxicological effects of heavy metals on 18 the humans? 19 MR. HEGARTY: Objection to 20 form. 21 THE WITNESS: Yes, I am. 22 BY MS. O'DELL: 23 Q. And what do you base that 24 statement on?</p>	<p style="text-align: right;">Page 493</p> <p>1 yes. 2 Q. And do the -- strike that 3 and start again. 4 Did Dr. Saed in the testing 5 that was done and reported in not only 6 the abstracts but also his manuscript, 7 involve Johnson's Baby Powder? 8 MR. HEGARTY: Objection to 9 form. 10 THE WITNESS: Yes. 11 Dr. Saed's did. Thank you for 12 reminding me. 13 BY MS. O'DELL: 14 Q. Was Dr. Longo and Rigler's 15 testing of historical samples of talcum 16 powder products produced in this 17 litigation, including Johnson's Baby 18 Powder and Shower to Shower? 19 A. Dr. Longo stated he did use 20 products over time from Johnson & Johnson 21 talcum powders. 22 Q. And was the evidence that 23 was presented in Hopkins Exhibit 28, did 24 it involve Johnson's talcum powder</p>

<p style="text-align: right;">Page 494</p> <p>1 products?</p> <p>2 A. Yes, it did.</p> <p>3 Q. Was evidence that you relied</p> <p>4 on in the form of Pier Exhibit 47, did</p> <p>5 those also involve talc that was taken</p> <p>6 from sources used to supply Johnson's</p> <p>7 talcum powder products?</p> <p>8 MR. SILVER: Objection to</p> <p>9 form.</p> <p>10 MR. HEGARTY: Objection to</p> <p>11 form.</p> <p>12 THE WITNESS: Dr. Pier?</p> <p>13 BY MS. O'DELL:</p> <p>14 Q. Yes.</p> <p>15 A. To my recollection, yes. If</p> <p>16 you'd like, I can look at the paper and</p> <p>17 confirm that.</p> <p>18 Q. Let me ask you about</p> <p>19 Dr. Blount. You were asked previously</p> <p>20 about her publication in 1991.</p> <p>21 Did Dr. Blount test</p> <p>22 Johnson's Baby Powder?</p> <p>23 A. Yes. But again, if I looked</p> <p>24 at the reference I could give you -- I</p>	<p style="text-align: right;">Page 496</p> <p>1 go.</p> <p>2 BY MS. O'DELL:</p> <p>3 Q. Did the FDA conclude in</p> <p>4 Exhibit 37 that -- well, let me just ask</p> <p>5 the question this way.</p> <p>6 If you'll turn to Page 2 of</p> <p>7 Exhibit 37, what was the FDA's conclusion</p> <p>8 regarding the testing that they had</p> <p>9 performed on the cosmetic powders?</p> <p>10 Doctor, I'll direct you to</p> <p>11 the second-to-the-last paragraph at the</p> <p>12 bottom of the page, the middle sentence.</p> <p>13 Do you see that, "Beginning for these</p> <p>14 reasons"?</p> <p>15 A. Yes, I see that.</p> <p>16 Q. And what was the FDA's</p> <p>17 conclusion?</p> <p>18 A. "For these reasons, while</p> <p>19 FDA finds these results informative, they</p> <p>20 do not prove that most or all talc or</p> <p>21 talc-containing cosmetic products that</p> <p>22 are currently or currently marketed in</p> <p>23 the United States are likely to be free</p> <p>24 of asbestos contamination."</p>
<p style="text-align: right;">Page 495</p> <p>1 could give you specifics.</p> <p>2 Q. Okay. And do you recall</p> <p>3 that that -- did -- let me just ask it</p> <p>4 this way.</p> <p>5 Did Dr. Blount find that</p> <p>6 there was asbestos in the Johnson's Baby</p> <p>7 Powder samples that she tested?</p> <p>8 A. Yes. To my recollection,</p> <p>9 she did, yes.</p> <p>10 Q. You were asked about some</p> <p>11 testing that had been done by the FDA on</p> <p>12 certain cosmetic powders. Do you</p> <p>13 remember that? It was Exhibit 37.</p> <p>14 MS. O'DELL: And is that in</p> <p>15 the bottom of that stack, 37?</p> <p>16 Thanks, Mark. If you'll</p> <p>17 hand those to me. I appreciate</p> <p>18 it.</p> <p>19 THE WITNESS: Sorry. My</p> <p>20 microphone.</p> <p>21 MS. O'DELL: Oh, did it come</p> <p>22 off?</p> <p>23 THE VIDEOGRAPHER: Raise it</p> <p>24 up as high as possible. There you</p>	<p style="text-align: right;">Page 497</p> <p>1 Q. You were also asked a number</p> <p>2 of questions regarding the FDA response</p> <p>3 to Dr. Epstein's letter in April of 2014,</p> <p>4 Exhibit 33.</p> <p>5 Do you recall those</p> <p>6 questions?</p> <p>7 A. I recall that questions were</p> <p>8 asked in this regard, yes.</p> <p>9 Q. While at this point in the</p> <p>10 day, I wouldn't expect you to recall the</p> <p>11 specific question, but you recall those</p> <p>12 general discussions?</p> <p>13 A. Yes, I do.</p> <p>14 Q. All right. Let me ask you,</p> <p>15 if you wouldn't mind, to turn to Page 3</p> <p>16 of -- of Exhibit 33.</p> <p>17 And the second paragraph.</p> <p>18 A. Starting, "The survey</p> <p>19 found"?</p> <p>20 Q. Yes. Yes, ma'am.</p> <p>21 And as of April 2014, was it</p> <p>22 the FDA's conclusion that their testing</p> <p>23 results did not prove that</p> <p>24 talc-containing cosmetic powders</p>

<p style="text-align: right;">Page 498</p> <p>1 currently marketed in the U.S. are free 2 of asbestos contamination? 3 MR. HEGARTY: Objection to 4 form. 5 THE WITNESS: Yes. I can 6 read the sentence, "While FDA 7 found this data informative, the 8 results were limited by the fact 9 that only four suppliers submitted 10 samples and the number of products 11 used. They do not prove that all 12 talc containing cosmetic products 13 currently marketed in the United 14 States are free of asbestos 15 contamination." 16 BY MS. O'DELL: 17 Q. Okay. While we are on this 18 Exhibit 33, Doctor, if you'll turn to 19 Page 5 of the exhibit. About two-thirds 20 of the way down, the paragraph beginning, 21 "While." 22 A. "While there exists no 23 direct proof?" 24 Q. Yes. And would you mind</p>	<p style="text-align: right;">Page 500</p> <p>1 causing ovarian cancer? 2 MR. HEGARTY: Objection to 3 form. 4 THE WITNESS: They are 5 consistent with my opinion, yes. 6 BY MS. O'DELL: 7 Q. Let me ask you if you would, 8 Doctor, to -- I'll do it for you. 9 Because it was marked here. 10 I'm going to hand to you the 11 Health Canada draft screening assessment 12 that was marked previously as Exhibit 9. 13 A. I see it. 14 Q. And let me ask you if you 15 would please, Doctor, first, did you 16 submit your report in this case prior to 17 Health Canada issuing the draft causal 18 assessment? 19 A. I submitted my -- my final 20 report November 15th or 16th. I'm not 21 quite clear on the date. And received 22 this or saw it for the first time in 23 January. So it did not go into my -- it 24 was not cited in my report and was not</p>
<p style="text-align: right;">Page 499</p> <p>1 reading, you know, the -- the -- those 2 first two sentences of that paragraph, 3 please? 4 A. "While there exists no 5 direct proof of talc and ovarian 6 carcinogenesis, the potential for 7 particulates to migrate from the 8 peritoneum" -- "the perineum and vagina 9 to the peritoneal cavity is 10 indisputable." 11 Q. And then if you'll read the 12 next sentence? 13 A. "It is, therefore, plausible 14 that perineal talc and other particulate 15 that reaches the endometrial cavity, the 16 fallopian tubes and ovaries and the 17 peritoneum may elicit a foreign body-type 18 reaction and an inflammatory response 19 that in some exposed women may progress 20 to epithelial cancers." 21 Q. And are those statements 22 written by the FDA consistent with your 23 opinions regarding the biologic 24 plausibility of talcum powder products</p>	<p style="text-align: right;">Page 501</p> <p>1 reviewed for my report. 2 Q. And by virtue of the fact 3 that came out after your report, did -- 4 did the health -- strike that and start 5 again. 6 Did the Health Canada 7 assessment inform your opinions in this 8 case? 9 A. It -- it could not have 10 informed my opinion that's written out in 11 the report. It was compelling evidence 12 that helped support the opinion that I 13 came to. 14 Q. Did it confirm your 15 opinions? 16 MR. HEGARTY: Objection to 17 form. 18 THE WITNESS: Yes. It 19 confirmed my opinions on many 20 lines, including methodology. 21 BY MS. O'DELL: 22 Q. If you'll look at Page 18 of 23 the assessment. 24 A. Yes. I see it.</p>

<p style="text-align: right;">Page 502</p> <p>1 Q. And looking at the 2 literature that is cited in this section, 3 did you cite in support of your opinions 4 Keskin 2009? 5 A. Keskin 2009, yes. 6 Q. And did you -- of course we 7 talked about it before. You cited 8 Penninkilampi 2018? 9 A. Yes, I did. 10 Q. And did you cite other 11 references included in the mode of action 12 discussion that was undertaken by Health 13 Canada on Pages 18, 19 and, you know, 20 14 of the Health Canada assessment? 15 A. Yes, I did. Do you want me 16 to tell you which ones? 17 Q. Just give us a few. Just 18 give us a few. 19 A. Henderson 1971. These are 20 the ones that come to mind readily. 21 Edelstam 1997. Egli and Newton 1961. De 22 Boer in 1972. Venter and Iturralde, 23 1979. Heller 1996. Cramer in 2007. 24 Would you like me to go on?</p>	<p style="text-align: right;">Page 504</p> <p>1 mechanism for the cause of cancer? 2 MR. HEGARTY: Objection to 3 form. 4 THE WITNESS: Biological 5 plausibility. 6 BY MS. O'DELL: 7 Q. They -- let me ask a better 8 question. Did they -- did they discuss 9 chronic inflammation, inflammation as a 10 biologically plausible mechanism for the 11 development of ovarian cancer? 12 A. Yes, they did. 13 Q. Did they discuss the role of 14 reactive oxygen species as part of the 15 biologically plausible mechanism of talc 16 in the development of ovarian cancer? 17 MR. HEGARTY: Objection to 18 form. 19 THE WITNESS: Oxidative 20 stress, yes. Yeah. React -- ROS. 21 Oxidative stress. 22 May I give the statement? 23 BY MS. O'DELL: 24 Q. Yes.</p>
<p style="text-align: right;">Page 503</p> <p>1 Q. So it's fair to say that 2 many of the references that you read, 3 reviewed, relied on in your report are 4 some of the same studies that Health 5 Canada relied on in their causal 6 assessment? 7 MR. HEGARTY: Objection to 8 form. 9 THE WITNESS: Yes. This was 10 very validating for my -- my 11 report in my opinion. 12 BY MS. O'DELL: 13 Q. Were you aware of the -- of 14 the assessment prior to it being issued 15 to the public? 16 A. Not at all. It was -- it 17 came out in late 2018, in December. 18 Q. In the assessment that was 19 undertaken by Health Canada, did they 20 assign any numerical weights in the 21 causal assessment to certain studies? 22 A. No, they do not. 23 Q. Did they discuss 24 inflammation as a sort of recognized</p>	<p style="text-align: right;">Page 505</p> <p>1 A. With respect to talc, 2 specifically local chronic irritation 3 leading to inflammatory response is one 4 possible mechanism of tumor progression 5 that is frequently hypothesized. 6 Q. And that's consistent with 7 your -- with your opinion in this case? 8 MR. HEGARTY: Objection to 9 form. 10 THE WITNESS: Yes. 11 BY MS. O'DELL: 12 Q. Is that consistent with your 13 opinion in this case? 14 A. Yes, it is. 15 Q. Did they discuss migration 16 as part of the biologically plausible 17 mechanism for the connection between 18 perineal use of talc and development of 19 ovarian cancer? 20 A. Yes, they did. 21 Q. Okay. Did they, on Page 15 22 and 16, did they discuss some of the 23 animal studies that you reference and 24 rely on in reaching your opinions in this</p>

<p style="text-align: right;">Page 506</p> <p>1 case?</p> <p>2 A. Yes, they do.</p> <p>3 MR. HEGARTY: Objection to</p> <p>4 form.</p> <p>5 THE WITNESS: And --</p> <p>6 BY MS. O'DELL:</p> <p>7 Q. Excuse me.</p> <p>8 A. They include Hamilton et</p> <p>9 al., 1984. Keskin 2009. Hamilton 1984</p> <p>10 again. Keskin again.</p> <p>11 Q. Okay. And if you'll turn to</p> <p>12 Page 21. You'll see at the top of the</p> <p>13 page, they have a section on biologic</p> <p>14 plausibility.</p> <p>15 A. Yes, they do.</p> <p>16 Q. Is -- is their discussion of</p> <p>17 biological plausibility as outlined on</p> <p>18 Page 21 consistent with your opinions in</p> <p>19 this case?</p> <p>20 MR. HEGARTY: Objection to</p> <p>21 form.</p> <p>22 THE WITNESS: Definitely</p> <p>23 consistent. Particles of talc are</p> <p>24 hypothesized to migrate into the</p>	<p style="text-align: right;">Page 508</p> <p>1 Q. Counsel directed your</p> <p>2 attention to the sentence -- counsel for</p> <p>3 Johnson & Johnson -- direct -- directed</p> <p>4 your attention to the sentence near the</p> <p>5 bottom of the left column.</p> <p>6 A. An important finding of this</p> <p>7 study is that talc use?</p> <p>8 Q. Yeah, the -- the potential</p> <p>9 mechanism by which genital talc is</p> <p>10 associated with an increased risk of</p> <p>11 ovarian cancer --</p> <p>12 A. I'm sorry. Again,</p> <p>13 discussion on the left side?</p> <p>14 Q. Yes. At the bottom of the</p> <p>15 first paragraph, the last sentence.</p> <p>16 A. Okay. I'm sorry.</p> <p>17 "Potential mechanism by which general</p> <p>18 talc associated with an increased risk of</p> <p>19 ovarian cancer hence remains unclear."</p> <p>20 Q. And Johnson & Johnson's</p> <p>21 counsel asked you about that sentence.</p> <p>22 A. Yes, they did.</p> <p>23 Q. But they didn't ask you</p> <p>24 about other sentences in this -- this</p>
<p style="text-align: right;">Page 507</p> <p>1 pelvis and ovarian tissue causing</p> <p>2 irritation and inflammation. And</p> <p>3 the presence of talc in the</p> <p>4 ovaries as I discussed previously</p> <p>5 has been documented by Heller in</p> <p>6 1996.</p> <p>7 BY MS. O'DELL:</p> <p>8 Q. Great. Thank you.</p> <p>9 Doctor, you were also asked</p> <p>10 some questions about the Penninkilampi</p> <p>11 paper.</p> <p>12 Do you recall those?</p> <p>13 A. I do recall being asked,</p> <p>14 yeah, from that.</p> <p>15 Q. Potentially the most</p> <p>16 difficult name to pronounce in the</p> <p>17 litigation.</p> <p>18 The Penninkilampi paper</p> <p>19 was -- was marked as Exhibit 34. Do you</p> <p>20 recall that?</p> <p>21 A. I see, I see it here. Yes.</p> <p>22 Q. And if I can ask you to turn</p> <p>23 to Page 45.</p> <p>24 A. I see Page 45.</p>	<p style="text-align: right;">Page 509</p> <p>1 paper, fair?</p> <p>2 A. That's fair.</p> <p>3 Q. So if you'll look to the</p> <p>4 right column on Page 45. Do you see the</p> <p>5 sentence beginning "if chronic</p> <p>6 inflammation"?</p> <p>7 A. I do. "If chronic</p> <p>8 inflammation due to ascending foreign</p> <p>9 bodies is indeed the mechanism by which</p> <p>10 talc use is associated with increased</p> <p>11 ovarian cancer risks, then the results</p> <p>12 fit the picture."</p> <p>13 Q. Is -- is that statement that</p> <p>14 the authors of the Penninkilampi study</p> <p>15 included in their report, excuse me, in</p> <p>16 their article, is that consistent with</p> <p>17 your opinions in this case?</p> <p>18 A. It is consistent.</p> <p>19 Q. And does it confirm the</p> <p>20 opinions that you reached in this case?</p> <p>21 A. It acts to confirm, yes, it</p> <p>22 does.</p> <p>23 Q. Okay. You were asked</p> <p>24 about -- a number of questions about</p>

<p style="text-align: right;">Page 510</p> <p>1 asbestos and the specific amount of 2 asbestos that would be introduced with 3 the perineal application of -- of talc. 4 A. Yes -- 5 Q. And let me ask you -- 6 A. -- I recall. 7 Q. You recall those questions? 8 A. Yes, I do. 9 Q. Is there any safe level of 10 asbestos -- 11 MR. HEGARTY: Objection to 12 form. 13 BY MS. O'DELL: 14 Q. -- in the perineum? 15 A. My opinion and conclusion is 16 no. 17 Q. Is asbestos a known potent 18 carcinogen? 19 A. It is. According -- 20 Q. Excuse me. Please go ahead. 21 A. According to the regulators 22 and the documents, it is, yes, a known 23 carcinogen, and it's extremely potent. 24 If you look at the effects that it causes</p>	<p style="text-align: right;">Page 512</p> <p>1 deposition of Robert Glenn in your 2 report? 3 A. I'm sorry, the deposition of 4 who? 5 Q. Robert Glenn. Page 6, about 6 midway down. 7 A. Yes, I did. "Because 8 asbestos is a known carcinogen, its 9 presence in cosmetic talc is 10 unacceptable, FDA 2012, FDA 2015." 11 Q. And do you recall that -- 12 was Mr. Glenn a former director of the 13 National Institute for Occupational 14 Safety and Health or NIOSH? 15 A. Yes. 16 Q. And what did Mr. Glenn 17 testify to regarding the presence of 18 asbestos in talc-based products? 19 A. He says, "As stated in a 20 recent deposition, that if there were a 21 fiber of asbestos in talcum-based 22 products, it would certainly 'provide a 23 biologically plausible mechanism for 24 increased lung disease' and that he</p>
<p style="text-align: right;">Page 511</p> <p>1 and at the dose levels that it causes 2 these effects. 3 Q. And of course IARC has -- 4 A. IARC has classified it as a 5 Class 1A. 6 Q. And did you review and rely 7 on IARC's conclusion regarding asbestos? 8 A. I did. 9 Q. Excuse me. And its 10 contribution to the -- to the development 11 of ovarian cancer? 12 A. Yes, I did. 13 Q. Did you review and rely on 14 IARC's conclusions regarding fibrous talc 15 or talc in an asbestiform habit regarding 16 its ability to cause ovarian cancer? 17 MR. HEGARTY: Objection to 18 form. 19 THE WITNESS: I did. 20 BY MS. O'DELL: 21 Q. If you'll turn to Page 6 in 22 your report. 23 A. Yes, I see it. 24 Q. Did you -- did you cite the</p>	<p style="text-align: right;">Page 513</p> <p>1 suspected that it would also have a 2 similar mechanism of disease in other 3 tissues and organs." 4 Q. And you were asked a number 5 of questions about the different 6 constituents of talcum powder products. 7 A. Yes. 8 Q. If talcum powder products 9 did not contain asbestos, would that 10 change your opinion about the biological 11 plausible mechanism of -- that explains 12 talc -- talc-based products causing 13 ovarian cancer? 14 A. No, it would not. 15 Q. You were asked questions 16 about a Dr. Neel from NYU. 17 A. The NYU Cancer Center. 18 Q. And you were asked if you 19 knew Dr. Neel. 20 A. Yes, I recall the question. 21 Q. And what's your 22 understanding of Dr. Neel's position? 23 A. My understanding is that he 24 is the chair -- he may not be called the</p>

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1 chair -- but he is the director of the
2 cancer center for NYU Langone Health and
3 NYU Medical School. It morphs into
4 different names.
5 Q. And in regard to the
6 toxicity of talcum powder products and
7 its effects, toxicological effects,
8 would -- would you be more knowledgeable
9 about those particular effects than a
10 clinician who diagnoses and treats
11 ovarian cancer?
12 MR. HEGARTY: Objection to
13 form.
14 BY MS. O'DELL:
15 Q. Like Dr. Neel?
16 A. I'm a toxicologist, and so
17 my main area of focus and understanding
18 and literature has to do with toxicology,
19 toxicological mechanisms, toxicological
20 effects.
21 Q. So --
22 A. So my knowledge base in
23 those areas would -- I would suspect very
24 strongly would exceed that of Dr. Neel's,

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1 who is a clinician.
2 Q. You were asked some
3 questions about the Shukla paper.
4 A. Yes.
5 Q. And -- and the Shukla paper
6 involved the use of talcum powder?
7 A. Yes.
8 Q. And if the --
9 A. Do you recall what exhibit
10 that was?
11 Q. I think it was the last
12 exhibit.
13 A. May I have a copy?
14 Q. 48. And did the Shukla
15 study involve the testing of, or the use
16 of talcum powder?
17 A. Yes. As they call it,
18 non-fibrous talc.
19 Q. And if the talcum powder
20 used in the Shukla study contained
21 nickel, that would be -- the data that
22 was reported in that study would be
23 relevant for the effects of nickel, fair?
24 MR. HEGARTY: Objection to

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1 form.
2 THE WITNESS: Could you
3 clarify that question?
4 BY MS. O'DELL:
5 Q. Yeah. It was a bad
6 question. I'm sorry. I'm getting tired.
7 A. If you're asking -- would
8 you like to ask -- rephrase it, or should
9 I give you my thought of what you were
10 trying to ask?
11 Q. Well, why don't you
12 interpret my question, and I'll follow
13 up.
14 A. If you're asking me if
15 nickel was a component of the non-fibrous
16 talc, then was nickel also in place when
17 it was treated, when the cells were
18 treated?
19 Q. That's correct.
20 A. Yes, if nickel was in the
21 non-fibrous talc then, yes, it was also
22 there when the cells were being exposed.
23 Q. And so -- and that would be
24 true of chromium and cobalt?

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1 A. Yes.
2 Q. And so, the results from the
3 Shukla study would have bearing on the
4 effect of those heavy metals if contained
5 in talcum powder?
6 MR. HEGARTY: Objection to
7 form.
8 THE WITNESS: Yes, if they
9 were -- yes, as constituents, they
10 would -- I would imagine and know
11 that they would play -- they could
12 be playing a role in the
13 toxicity -- the cell toxicity or
14 the gene expression changes that
15 were observed.
16 BY MS. O'DELL:
17 Q. Thank you. And in regard to
18 your opinions related to cobalt,
19 chromium, and nickel, you were asked a
20 number of questions about whether there
21 were any human studies measuring the
22 effect of -- of nickel at -- in the
23 ovary. Do you recall that?
24 A. I recall that question --

<p style="text-align: right;">Page 518</p> <p>1 those questions.</p> <p>2 Q. Would it be possible to</p> <p>3 design a study in humans where nickel was</p> <p>4 deposited at their ovary to see if a</p> <p>5 female would develop ovarian cancer?</p> <p>6 A. I think I answered and said</p> <p>7 that would be ridiculous in the sense</p> <p>8 that this would be totally unethical to</p> <p>9 take a known carcinogen or a classified</p> <p>10 1A carcinogen and use it for experimental</p> <p>11 studies in humans by placing it in the</p> <p>12 perineal -- or anywhere within the body</p> <p>13 intentionally.</p> <p>14 Q. And would that also be true</p> <p>15 for similar reasons for cobalt and</p> <p>16 chromium?</p> <p>17 A. Yes.</p> <p>18 Q. Would the same also be true</p> <p>19 of designing a study that applied</p> <p>20 asbestos to a female's ovary for purposes</p> <p>21 of seeing if she developed cancer?</p> <p>22 A. I'm smiling because it holds</p> <p>23 true for any -- any known or suspected</p> <p>24 carcinogen cannot be used intentionally</p>	<p style="text-align: right;">Page 520</p> <p>1 IRBs.</p> <p>2 Q. Okay. You looked at, as I</p> <p>3 understand it, for your purposes of your</p> <p>4 task in this case, you looked at the</p> <p>5 issue of biologic plausibility for</p> <p>6 perineal talc use and ovarian cancer.</p> <p>7 A. Yes, I did.</p> <p>8 Q. Did you -- did you -- was</p> <p>9 that inquiry focused on epithelial</p> <p>10 ovarian cancer in particular?</p> <p>11 A. It -- it was -- most, if not</p> <p>12 all the studies I looked at in animals</p> <p>13 and -- were associated with epithelial</p> <p>14 ovarian cancer.</p> <p>15 Some studies in humans did</p> <p>16 look -- did break out the differences.</p> <p>17 Q. Let me ask you if you</p> <p>18 wouldn't mind, to turn to Page 8 of your</p> <p>19 report. And you'll look at the top of</p> <p>20 the page. In the first full paragraph,</p> <p>21 middle of the -- that paragraph discusses</p> <p>22 Dr. Longo and Rigler's recent report that</p> <p>23 reports that talcum powder products</p> <p>24 manufactured by Johnson's Baby Powder and</p>
<p style="text-align: right;">Page 519</p> <p>1 on a human being for testing. It's</p> <p>2 unethical, and would probably in all</p> <p>3 likelihood not be approved by the</p> <p>4 institutional review board of academic</p> <p>5 institutions or any reputable scientists.</p> <p>6 Q. Would that be true of</p> <p>7 fibrous talc?</p> <p>8 MR. HEGARTY: Objection to</p> <p>9 form.</p> <p>10 BY MS. O'DELL:</p> <p>11 Q. You may answer.</p> <p>12 A. That would be true of</p> <p>13 fibrous talc.</p> <p>14 Q. Would it be true of platy</p> <p>15 talc, if there is such a thing as pure</p> <p>16 platy talc?</p> <p>17 A. If there is a -- if there is</p> <p>18 any suspicion that any product, including</p> <p>19 platy talc, might be involved in</p> <p>20 producing inflammation or any other type</p> <p>21 of adverse health effect, then it would</p> <p>22 be very unethical to go ahead and</p> <p>23 intentionally use that in a human study,</p> <p>24 in my opinion, and in the opinion of most</p>	<p style="text-align: right;">Page 521</p> <p>1 Shower to Shower have contained and</p> <p>2 continue to contain asbestos. Do you see</p> <p>3 that sentence?</p> <p>4 A. Yes, I do.</p> <p>5 Q. And then it goes on, you go</p> <p>6 on to report his results from test of</p> <p>7 samples manufactured from the 1960s and</p> <p>8 1990s.</p> <p>9 A. Through -- through the</p> <p>10 1990s.</p> <p>11 Q. Through the 1990s, that's</p> <p>12 correct.</p> <p>13 And you -- you have a</p> <p>14 footnote here to Footnote 7?</p> <p>15 A. Yes.</p> <p>16 Q. And Dr. Longo and Rigler's</p> <p>17 report is noted in the footnote and it's</p> <p>18 dated November 14, 2018.</p> <p>19 A. Yes.</p> <p>20 Q. Do you see that?</p> <p>21 A. Yes.</p> <p>22 Q. And just, did you have in</p> <p>23 your possession and review Dr. Rigler and</p> <p>24 Longo's November 14, 2018, report during</p>

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1 the completion of your own report?
2 A. I had it available prior to
3 the submission of my final report, yes.
4 The only thing I did not
5 have was the December 2018 supplement.
6 Q. His most recent supplement?
7 A. His most recent supplement,
8 yes.
9 Q. I think just to be clear,
10 that -- was his most recent supplemental
11 report you're referring to, was that the
12 report dated in January, I think 16th or
13 15th of this month?
14 A. It was sometime in January.
15 Q. Okay.
16 A. Yes. I could answer that
17 question specifically if I saw the
18 exhibit.
19 Q. And I've handed you what's
20 been marked I think as Exhibit --
21 A. 3.
22 Q. 3. And is Exhibit 3 the
23 supplemental report --
24 A. Yes, it is.

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1 Q. -- that you reviewed
2 recently?
3 A. I'm sorry, yes.
4 Q. And what's the date on the
5 report?
6 A. January 15, 2019.
7 MS. O'DELL: Okay. I have
8 nothing further, Doctor. Thank
9 you.
10 MR. HEGARTY: Take a break.
11 I need to use the restroom.
12 THE VIDEOGRAPHER: The time
13 is 8:10 p.m. Going off the
14 record.
15 (Short break.)
16 THE VIDEOGRAPHER: We are
17 back on the record. The time is
18 8:16 p.m.
19 - - -
20 EXAMINATION
21 - - -
22 BY MR. HEGARTY:
23 Q. Dr. Zelikoff, I have some
24 questions in follow-up to the questions

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1 that Ms. O'Dell asked you.
2 First of all, you were
3 referred to Page 12 of your report
4 under -- under Section C, Fragrances.
5 Would you go to that portion of your
6 report please?
7 A. I will, thank you. Yes.
8 I'm here.
9 Q. You were asked about this
10 part of your report being identical to
11 the same part of Smith-Bindman's report.
12 Do you recall being asked those
13 questions?
14 MS. O'DELL: Object to the
15 form.
16 THE WITNESS: Smith --
17 Smith-Bindman report? I'm sorry,
18 I don't recall -- oh, in the
19 beginning of the deposition?
20 BY MR. HEGARTY:
21 Q. Yes.
22 A. Okay. That was a long time
23 ago.
24 Q. First of all, are you aware

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1 that Dr. Crowley has been deposed in this
2 litigation?
3 A. Yes.
4 Q. Did you read his deposition?
5 A. I did.
6 Q. When did you read his
7 deposition?
8 A. I'm sorry, I don't recall
9 the exact date.
10 May I see Dr. Crowley's
11 deposition?
12 Q. Well, I just asked you if
13 you had read it. That's my only
14 question.
15 Other than Dr. Crowley's
16 deposition, have you read the depositions
17 of any other plaintiffs' experts deposed
18 in the MDL, this litigation?
19 A. Any of the other plaintiffs'
20 depositions?
21 Q. Correct.
22 A. Dr. Dydek.
23 Q. Anybody else?
24 A. I'm looking to see the

<p style="text-align: right;">Page 526</p> <p>1 others.</p> <p>2 Q. It's at the end of Exhibit</p> <p>3 B.</p> <p>4 A. Okay. Thank you. Thank</p> <p>5 you.</p> <p>6 Q. Well, my question -- let me</p> <p>7 ask a different question. Let me ask</p> <p>8 whether you have reviewed the MDL</p> <p>9 depositions; that is, the depositions</p> <p>10 that plaintiffs' experts have taken in</p> <p>11 this litigation over their expert reports</p> <p>12 besides Dr. Crowley?</p> <p>13 MS. O'DELL: Object to form.</p> <p>14 THE WITNESS: Dr. Longo.</p> <p>15 Sorry.</p> <p>16 BY MR. HEGARTY:</p> <p>17 Q. Dr. Longo has not yet been</p> <p>18 deposed in --</p> <p>19 A. I read his report.</p> <p>20 Q. -- for his MDL report.</p> <p>21 No, I'm talking about the</p> <p>22 deposition --</p> <p>23 A. I'm sorry.</p> <p>24 Q. -- of an expert who has</p>	<p style="text-align: right;">Page 528</p> <p>1 Q. Page 12.</p> <p>2 A. "There are more than 150</p> <p>3 different chemicals"?</p> <p>4 Q. Those four sentences, or</p> <p>5 three -- or strike that.</p> <p>6 The second sentence in that</p> <p>7 section is not in Dr. Crowley's report.</p> <p>8 He did not write, "I reviewed the expert</p> <p>9 report of Dr. Michael Crowley that</p> <p>10 concludes that some of these chemicals</p> <p>11 may contribute to the inflammatory</p> <p>12 response, toxicity, and potential</p> <p>13 toxicity of Johnson & Johnson's talcum</p> <p>14 powder products."</p> <p>15 MS. O'DELL: Objection.</p> <p>16 BY MR. HEGARTY:</p> <p>17 Q. That sentence is not in</p> <p>18 Dr. Crowley's report?</p> <p>19 MS. O'DELL: Objection.</p> <p>20 THE WITNESS: I'm terribly</p> <p>21 sorry. I'm going to silence that</p> <p>22 or we can and talk over it.</p> <p>23 MS. O'DELL: Go ahead and</p> <p>24 silence it.</p>
<p style="text-align: right;">Page 527</p> <p>1 been -- who is being deposed about their</p> <p>2 report in the MDL.</p> <p>3 You said Dr. Crowley. Have</p> <p>4 you read anyone else's deposition that</p> <p>5 have discussed their report in the MDL?</p> <p>6 MS. O'DELL: I think there</p> <p>7 may be some confusion between</p> <p>8 report and deposition.</p> <p>9 THE WITNESS: Yes. There</p> <p>10 was.</p> <p>11 BY MR. HEGARTY:</p> <p>12 Q. Did you read Dr. Crowley's</p> <p>13 deposition over his report?</p> <p>14 A. I read Dr. Crowley's report.</p> <p>15 I'm sorry. I stand corrected.</p> <p>16 Q. Dr. Crowley's report does</p> <p>17 not contain the sentences that you've</p> <p>18 included under your Section C,</p> <p>19 fragrances, correct?</p> <p>20 MS. O'DELL: Object to the</p> <p>21 form.</p> <p>22 THE WITNESS: What page are</p> <p>23 we going back to, please?</p> <p>24 BY MR. HEGARTY:</p>	<p style="text-align: right;">Page 529</p> <p>1 (Brief interruption.)</p> <p>2 MR. HEGARTY: Let's go off</p> <p>3 the record.</p> <p>4 THE VIDEOGRAPHER: The time</p> <p>5 is 8:21 p.m. Off the record.</p> <p>6 (Whereupon, a discussion was</p> <p>7 held off the record.)</p> <p>8 THE VIDEOGRAPHER: The time</p> <p>9 is 8:21 p.m. Back on the record.</p> <p>10 BY MR. HEGARTY:</p> <p>11 Q. The second sentence under</p> <p>12 your section fragrances is nowhere in</p> <p>13 Dr. Crowley's report?</p> <p>14 A. That --</p> <p>15 MS. O'DELL: Objection to</p> <p>16 form.</p> <p>17 THE WITNESS: That sentence</p> <p>18 is not there, but I concluded that</p> <p>19 when he talked about the</p> <p>20 fragrances, I concluded that -- I</p> <p>21 inferred from his -- from his</p> <p>22 report, that these chemicals do</p> <p>23 contribute to the inflammatory</p> <p>24 response, toxicity and potential</p>

<p style="text-align: right;">Page 530</p> <p>1 carcinogenicity. 2 BY MR. HEGARTY: 3 Q. The sentence, "I concur with 4 his opinion," is not in Dr. Crowley's 5 report, is it? 6 A. No. That was my opinion. 7 Q. That same opinion, stated 8 exactly the same way, is in the 9 Dr. Smith-Bindman report, correct? 10 A. Can I see that report? 11 Q. Do you recall without 12 looking at it, that that same section is 13 in her report? 14 A. I do not. I do not recall. 15 Q. Okay. Did you -- do you 16 know -- have you ever spoken to 17 Dr. Smith-Bindman? 18 A. Not at all. 19 Q. Do you know who she is? 20 A. I don't. 21 Q. Do you know her expertise? 22 A. I do not. 23 Q. Have you ever heard her name 24 before today?</p>	<p style="text-align: right;">Page 532</p> <p>1 BY MR. HEGARTY: 2 Q. Doctor, you -- 3 A. -- that included talc. 4 Q. Doctor, you testified 5 earlier in this deposition that your 6 information as it relates to talc and 7 ovarian cancer came from the media and 8 discussion with colleagues, correct? 9 A. Prior to being contacted. 10 Q. Right. So prior to being 11 contacted for counsel for plaintiffs, you 12 had no expertise in talc and ovarian 13 cancer, correct? 14 A. As a toxicologist -- I'm 15 sorry. I'm getting hung up on the word 16 "expert" as you're using it. As a 17 toxicologist, I am familiar with talc. I 18 am familiar with much of the toxicity of 19 it. But the primary -- in discussing 20 talc and its relationship to cancer, it 21 was through colleagues and the media, 22 yes, correct. 23 Q. You had not studied, prior 24 to being contacted by plaintiffs'</p>
<p style="text-align: right;">Page 531</p> <p>1 A. Not -- not to my knowledge. 2 But I would like to see -- to refresh my 3 memory, if it's available. 4 Q. You were asked about your 5 expertise as it relates to talc and 6 inflammation. Before you were contacted 7 by Ms. Emmel, you had no expertise in 8 talc, correct? 9 MS. O'DELL: Objection to 10 form. 11 THE WITNESS: I performed no 12 scientific studies in it. 13 BY MR. HEGARTY: 14 Q. You also reviewed no 15 scientific studies concerning talc, 16 correct? 17 MS. O'DELL: Objection to 18 form. 19 THE WITNESS: I have 20 reviewed papers. I am editor and 21 associate editor on an editorial 22 board so that in my past 23 experience, I likely reviewed 24 papers --</p>	<p style="text-align: right;">Page 533</p> <p>1 counsel, any issues reported in the 2 medical literature with regard to talc 3 and ovarian cancer, correct? 4 A. I have not studied in my 5 laboratory, that's correct. 6 Q. You also did not review any 7 literature discussing talc and ovarian 8 cancer prior to being contacted by 9 counsel for plaintiff? 10 A. That is correct. 11 Q. Prior to being contacted by 12 counsel for plaintiffs you had not 13 studied the toxicology -- toxic aspects, 14 if any, of talc, correct? 15 MS. O'DELL: Object to the 16 form. 17 THE WITNESS: I have -- as I 18 stated, I have reviewed papers 19 that have looked at it. And I've 20 reviewed them for acceptance into 21 journals. 22 BY MR. HEGARTY: 23 Q. Can you cite for us today 24 any such papers?</p>

<p style="text-align: right;">Page 534</p> <p>1 A. Over my career, I cannot. 2 Sorry. 3 Q. Can you identify any study 4 you have published that investigated or 5 discussed the toxicity of cobalt? 6 A. I've written review articles 7 on the toxicology of metals in general 8 and cobalt was in there, and in book 9 chapters. 10 Q. But it's your testimony that 11 you have written review papers where you 12 discussed the toxicity of cobalt? 13 A. I did not say review papers. 14 I said book chapters. 15 Q. So you had written a book 16 chapter to discuss the toxicity of 17 cobalt? 18 MS. O'DELL: Objection to 19 form. 20 THE WITNESS: I was an 21 editor of a book, several books -- 22 two books actually, which looked 23 at the toxicity of cobalt -- 24 looked at the toxicity of metals.</p>	<p style="text-align: right;">Page 536</p> <p>1 nickel? 2 A. Yes. 3 Q. What published article have 4 you -- have you written discussing the 5 toxicity of nickel? 6 A. One that comes to my mind, 7 without looking at my CV, is an early 8 publication associated with the 9 immunology and immunotoxicity of nickel 10 in fish. 11 Q. What nickel -- was it a 12 nickel compound? 13 A. It was a nickel chloride, a 14 soluble nickel compound. 15 Q. Are nickel compounds in 16 Johnson's Baby Powder? 17 A. Nickel -- according to the 18 J&J documents and other -- other internal 19 documents, yes. 20 Q. Okay. What nickel compounds 21 are in Johnson's Baby Powder? 22 A. The report indicates nickel. 23 It does not break it down to a particular 24 salt or a particular compound of nickel.</p>
<p style="text-align: right;">Page 535</p> <p>1 And cobalt, to my recollection, 2 was in both of those books. 3 BY MR. HEGARTY: 4 Q. Did you write those 5 chapters? 6 A. I reviewed those chapters 7 for publication in those books. 8 Q. My question was did you 9 write those chapters? 10 A. I'm sorry. Did I write 11 those chapters on cobalt? No, I did not. 12 Q. Have you ever written any 13 published chapter or article discussing 14 the toxicity of cobalt? 15 A. I have not -- 16 MS. O'DELL: Objection. 17 THE WITNESS: -- written an 18 article in the area of cobalt, but 19 I am familiar with metals, very 20 much so from the department and 21 the research that I do. 22 BY MR. HEGARTY: 23 Q. Have you written any 24 published article discussing toxicity of</p>	<p style="text-align: right;">Page 537</p> <p>1 Q. Have you written any papers 2 looking at the toxicity of chromium-3? 3 A. I'm going to look in my -- 4 in my CV. 5 Q. Well, without looking at 6 your CV, for purposes of time, can you 7 recall any such article? 8 MS. O'DELL: If you need to 9 take a moment, Doctor, feel free 10 to. 11 MR. HEGARTY: We'll go off 12 the record if she needs to take a 13 moment. 14 BY MR. HEGARTY: 15 Q. Because I qualified my 16 question by asking you, without looking 17 at your CV, are you able to cite an 18 article that you've written? 19 A. I want to give actual data 20 to you. In my mind, I recall a paper 21 that I wrote with Dr. Max Costa on 22 chromium. And -- and possibly with Toby 23 Rossman. But without looking, I can't be 24 absolutely sure.</p>

<p style="text-align: right;">Page 538</p> <p>1 Q. You refer over on pages -- 2 or on Page 25 of your report -- 3 A. Yes. 4 Q. -- to -- 5 A. Talc-induced inflammation. 6 Q. Well, let me finish my 7 question. 8 A. Oh, I'm sorry. 9 Q. You refer over on Page 25 in 10 the fourth paragraph to an abstract and 11 other material by Dr. Harper and 12 Dr. Saed, correct? 13 A. Yes. In the last -- in the 14 last paragraph, in the last sentence. 15 Q. And none of those 16 publications refer to testing using 17 Johnson's Baby Powder, correct? 18 MS. O'DELL: Objection to 19 form. 20 THE WITNESS: To my 21 knowledge, no, but I would have to 22 look at the paper to be absolutely 23 sure. But they did use talc, 24 yes -- talcum powder.</p>	<p style="text-align: right;">Page 540</p> <p>1 the statements that you were asked about 2 by plaintiffs' counsel in your expert 3 report, correct? 4 MS. O'DELL: Object to form. 5 THE WITNESS: Not without 6 checking my document, I can't 7 answer conclusively. 8 BY MR. HEGARTY: 9 Q. You did not rely on this 10 portion of the FDA's letter for purposes 11 of your opinions in this case, correct? 12 MS. O'DELL: Regarding the 13 asbestos testing? 14 BY MR. HEGARTY: 15 Q. The portion that I just 16 referred you to, the top two paragraphs 17 at Page 3. 18 A. They do not prove that all 19 talc-containing cosmetic products 20 currently marketed in the United States 21 are free of asbestos. Is that -- 22 Q. Yes. 23 A. Okay. And the question was? 24 Q. You did not refer to that</p>
<p style="text-align: right;">Page 539</p> <p>1 BY MR. HEGARTY: 2 Q. Can you cite for me any 3 animal or cell studies that you reviewed 4 for purposes of preparing your report 5 that tested Johnson's Baby Powder other 6 than Dr. Saed's recent manuscript? 7 A. I know I have, I just can't 8 recall. 9 You are talking about 10 publications, correct? 11 Q. Yes. That you've cited in 12 your report. 13 A. I can't find it at the 14 moment, so I would have to say no. 15 Q. Did you find Exhibit 33, the 16 FDA's response letter to Dr. Epstein. 17 A. Thank you. 18 Q. You were referred to Page 3 19 in FDA's statement with regard to its 20 testing of samples of cosmetic grade raw 21 material talc and cosmetic products for 22 asbestos? 23 A. Yes, I did. 24 Q. You did not refer to any of</p>	<p style="text-align: right;">Page 541</p> <p>1 statement in your report, correct? 2 A. That is correct, yes. 3 Q. Also you did not cite on 4 Page 5 in your report the statement that 5 "it is, therefore, plausible that 6 perineal talc and other particulate that 7 reaches the endometrial cavity, et 8 cetera, may elicit foreign body-type 9 reaction and inflammatory response that 10 in some exposed women may progress to 11 epithelial cancers." 12 You did not cite that 13 sentence in your report either, correct? 14 A. I did not -- 15 MS. O'DELL: Objection to 16 form. 17 THE WITNESS: I did not cite 18 that sentence in my report either. 19 However, this document was in 20 my -- in my citations in the 21 overall reliance -- reliance 22 document. 23 BY MR. HEGARTY: 24 Q. With regard to the draft</p>

<p style="text-align: right;">Page 542</p> <p>1 screening assessment by Canada, Canada 2 employs a precautionary principle. Are 3 you aware of that? 4 A. Yes. 5 Q. Do you know what a 6 precautionary principle is? 7 A. I do know what a 8 precaution -- 9 Q. What is it? 10 A. A precautionary principle is 11 one where you -- in my -- in my opinion 12 and what -- to my knowledge, it's a 13 principle in which you use every 14 precaution in terms of assessment, in 15 terms of use in animal models and human 16 models. You follow precaution. 17 Q. Okay. The draft screenings 18 assessment, Exhibit Number 9, contains 19 the following statement -- and I only -- 20 I only have your copy. 21 A. Oh okay. 22 Q. I'm going to read it to you 23 and tell me whether you agree with it. 24 A. Okay.</p>	<p style="text-align: right;">Page 544</p> <p>1 "The specific mechanisms and 2 cascade of molecular events by which talc 3 might cause ovarian cancer have not been 4 identified." 5 MS. O'DELL: Wait. Do you 6 mind showing Dr. Zelikoff? 7 MR. HEGARTY: Well, then I 8 won't have -- I'm just reading 9 this statement. 10 MS. O'DELL: Well, but if 11 you're reading from the draft 12 assessment -- 13 MR. HEGARTY: You know what, 14 I -- this is the only copy I have. 15 If you want to hand me your copy. 16 MR. TISI: I have my copy. 17 It has my notes on it. If you... 18 Do you want it? 19 MS. O'DELL: You're welcome 20 to my copy. 21 MR. HEGARTY: Thank you. 22 BY MR. HEGARTY: 23 Q. Page 18, second paragraph. 24 I was on Page 18, Doctor.</p>
<p style="text-align: right;">Page 543</p> <p>1 Q. "The etiology of most 2 ovarian tumors in general has not been 3 well established." 4 MS. O'DELL: What page are 5 you on, please? 6 MR. HEGARTY: Page 18. 7 BY MR. HEGARTY: 8 Q. Do you agree with that 9 statement? 10 A. Please read it again. 11 Q. "The etiology of most 12 ovarian tumors in general has not been 13 well established." 14 A. The etiology is -- has not 15 been well established. But it has been 16 studied. But there -- okay. I'm done. 17 Q. The -- on page -- strike 18 that. On Page 21 -- 19 A. Of my report? 20 Q. No, of the -- 21 A. Health Canada. 22 Q. -- health assessment states 23 the following statement and tell me 24 whether you agree with it.</p>	<p style="text-align: right;">Page 545</p> <p>1 A. You handed it to me like 2 this, sir. 3 Q. Right. On page -- I'm 4 sorry, Page 21. 5 A. This is Page 21. 6 Q. Sorry. Page 21, second 7 paragraph. The statement at the end 8 reads, "However, the specific mechanisms 9 and cascade of molecular events by which 10 talc might cause ovarian cancer have not 11 been identified." 12 Do you agree with that 13 statement? 14 MS. O'DELL: Objection to 15 form. 16 THE WITNESS: That's a 17 statement here. 18 BY MR. HEGARTY: 19 Q. Do you agree with that 20 statement? 21 A. Oh, I'm sorry. I'm sorry, 22 I've lost -- Page 21, what -- 23 Q. Page 21, second paragraph -- 24 A. -- what paragraph?</p>

<p style="text-align: right;">Page 546</p> <p>1 Under --</p> <p>2 Q. Last two lines.</p> <p>3 A. Under --</p> <p>4 Q. Under -- in the biologic</p> <p>5 plausibility section.</p> <p>6 A. I see it. Thank you.</p> <p>7 Q. It read -- the statement</p> <p>8 reads: The specific mechanisms and</p> <p>9 cascade of molecular events by which talc</p> <p>10 might cause ovarian cancer have not been</p> <p>11 identified.</p> <p>12 Do you agree with that</p> <p>13 statement?</p> <p>14 A. Yes, they have not been</p> <p>15 clearly and conclusively identified.</p> <p>16 Q. But that's not what that</p> <p>17 sentence reads. My question was do you</p> <p>18 agree with the sentence that I just read</p> <p>19 to you.</p> <p>20 A. It is -- I think it's a</p> <p>21 sentence taken out of text.</p> <p>22 Do I agree with the sentence</p> <p>23 as it is written? No. I would have to</p> <p>24 add the words, "have not been clearly</p>	<p style="text-align: right;">Page 548</p> <p>1 today it's not -- you're not using it to</p> <p>2 inform your opinions, correct?</p> <p>3 A. It is -- it is support and</p> <p>4 validation of my opinions.</p> <p>5 Q. You referenced IARC and its</p> <p>6 designation of asbestos. What has IARC</p> <p>7 designated talc for genital uses as?</p> <p>8 MS. O'DELL: Objection.</p> <p>9 THE WITNESS: I -- in -- in</p> <p>10 terms of classification, may I</p> <p>11 look at the document?</p> <p>12 BY MR. HEGARTY:</p> <p>13 Q. Well, they've designated</p> <p>14 talc used --</p> <p>15 A. Fibrous -- fibrous --</p> <p>16 Q. -- for perineal use as 2B,</p> <p>17 correct?</p> <p>18 A. 2B, yes. Fibrous talc,</p> <p>19 correct.</p> <p>20 Q. You were asked about the</p> <p>21 deposition of Robert Glenn, correct?</p> <p>22 A. The past manager and</p> <p>23 director of NIOSH.</p> <p>24 Q. Yes.</p>
<p style="text-align: right;">Page 547</p> <p>1 identified."</p> <p>2 Q. So you don't agree with</p> <p>3 everything in the --</p> <p>4 A. Or established.</p> <p>5 Q. So you don't agree with</p> <p>6 everything in Health Canada's risk</p> <p>7 assessment, correct?</p> <p>8 MS. O'DELL: Objection to</p> <p>9 form.</p> <p>10 THE WITNESS: I -- I do not</p> <p>11 agree with this sentence, correct.</p> <p>12 BY MR. HEGARTY:</p> <p>13 Q. You do rely on, for purposes</p> <p>14 of your opinions in this case, the draft</p> <p>15 screening assessment, correct?</p> <p>16 MS. O'DELL: Objection.</p> <p>17 THE WITNESS: No. That came</p> <p>18 out well after I handed in my</p> <p>19 final report, so it was not used</p> <p>20 to inform my opinion. It was</p> <p>21 supporting validation for my</p> <p>22 opinion.</p> <p>23 BY MR. HEGARTY:</p> <p>24 Q. So still -- still through</p>	<p style="text-align: right;">Page 549</p> <p>1 A. Yes.</p> <p>2 Q. Did you read the entirety of</p> <p>3 his deposition?</p> <p>4 A. No, I did not.</p> <p>5 Q. Did you agree with</p> <p>6 everything he said in his deposition?</p> <p>7 A. I said I did not read the</p> <p>8 entirety. I can't answer.</p> <p>9 (Document marked for</p> <p>10 identification as Exhibit</p> <p>11 Zelickoff-49.)</p> <p>12 BY MR. HEGARTY:</p> <p>13 Q. I'm going to mark as</p> <p>14 Exhibit 49, portions of the deposition of</p> <p>15 Dr. Robert Glenn. If you turn to the</p> <p>16 first page of that exhibit, Page 482.</p> <p>17 A. Page 482, yes.</p> <p>18 Q. Yes. Mr. Glenn was asked in</p> <p>19 the middle of the page, Lines 12 to 14,</p> <p>20 "Has the data also showed that talcum</p> <p>21 powder is not cytotoxic, meaning it</p> <p>22 doesn't damage cells?"</p> <p>23 Mr. Glenn answer's, "Yes."</p> <p>24 A. Yes.</p>

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<p>1 Q. Did you cite that portion of</p> <p>2 his testimony in your expert report?</p> <p>3 MS. O'DELL: Objection to</p> <p>4 form.</p> <p>5 THE WITNESS: No.</p> <p>6 BY MR. HEGARTY:</p> <p>7 Q. Did you read it?</p> <p>8 A. I said that I did not read</p> <p>9 this in its -- in its entirety.</p> <p>10 Q. Do you agree with that</p> <p>11 sentence?</p> <p>12 I'm sorry, do you agree with</p> <p>13 his answer to that question?</p> <p>14 MS. O'DELL: Objection to</p> <p>15 form.</p> <p>16 THE WITNESS: To the</p> <p>17 question, "Has the data also</p> <p>18 showed that talcum powder is not</p> <p>19 cytotoxic, meaning it doesn't</p> <p>20 damage cells?"</p> <p>21 So if the question is do I</p> <p>22 agree with that sentence -- do I</p> <p>23 agree with his answer of yes,</p> <p>24 there have been data showing, in</p>	<p>1 shows that talcum powder is not</p> <p>2 mutagenic? There is.</p> <p>3 Q. Did you cite that portion of</p> <p>4 Mr. Glenn's testimony in your report?</p> <p>5 A. No, I did not.</p> <p>6 Q. If you look at the next page</p> <p>7 at the top. The question, 2 through 7,</p> <p>8 with the answer on 8.</p> <p>9 A. Mm-hmm-hmm.</p> <p>10 Q. Did you cite that question</p> <p>11 and answer in your report?</p> <p>12 MS. O'DELL: Object to the</p> <p>13 form.</p> <p>14 THE WITNESS: I did not cite</p> <p>15 any of Dr. Glenn's information</p> <p>16 because I -- I did not read it in</p> <p>17 detail.</p> <p>18 BY MR. HEGARTY:</p> <p>19 Q. You can put that aside.</p> <p>20 Is it your testimony that</p> <p>21 you're more knowledgeable regarding talc</p> <p>22 and ovarian cancer than Dr. Neel?</p> <p>23 A. No, what my testimony is to</p> <p>24 is that I have extensive knowledge in</p>
Page 551	Page 553
<p>1 certain circumstances, in certain</p> <p>2 cell lines, that talcum powder has</p> <p>3 not been shown to be cytotoxic at</p> <p>4 certain concentrations.</p> <p>5 BY MR. HEGARTY:</p> <p>6 Q. Looking down at the next</p> <p>7 question, 18 through 21, he's asked, "And</p> <p>8 has the data also showed that talcum</p> <p>9 powder is not mutagenic, meaning it</p> <p>10 doesn't mutate genes?"</p> <p>11 "Answer: Yes."</p> <p>12 Do you agree with his answer</p> <p>13 to that question?</p> <p>14 A. I do not agree. I think</p> <p>15 that the -- I do not agree with his</p> <p>16 answer. I think that his -- that the</p> <p>17 question has to be -- the question in my</p> <p>18 opinion, it was ambiguous. And I'm not</p> <p>19 sure what he was basing that on in terms</p> <p>20 of his response.</p> <p>21 If you -- if he was looking</p> <p>22 at mutagenicity in terms of Ames assays</p> <p>23 or yes, they have not shown mutagenicity.</p> <p>24 So is there data that also</p>	<p>1 toxicological aspects, the cytotoxicity</p> <p>2 of it, and the inflammatory responses</p> <p>3 from an -- from an academic perspective</p> <p>4 and a biological mechanism perspective.</p> <p>5 Q. What is Dr. Neel's knowledge</p> <p>6 of the toxicological aspects and the</p> <p>7 toxicity of talc?</p> <p>8 A. I do not know.</p> <p>9 Q. What's his -- is he a</p> <p>10 cancer -- strike that.</p> <p>11 He is a cancer biologist,</p> <p>12 correct?</p> <p>13 MS. O'DELL: Objection to</p> <p>14 form.</p> <p>15 THE WITNESS: The only thing</p> <p>16 I know about Dr. Neel is that he</p> <p>17 is the director of the Cancer</p> <p>18 Institute. I am not familiar with</p> <p>19 his research.</p> <p>20 BY MR. HEGARTY:</p> <p>21 Q. Have you ever evaluated his</p> <p>22 qualifications?</p> <p>23 A. No. I was not on the search</p> <p>24 committee nor do I have access to his CV.</p>

<p style="text-align: right;">Page 554</p> <p>1 Q. You made statements 2 indicating that you believe that you are 3 more knowledgeable than Dr. Neel 4 regarding the toxicities of talc. Is 5 that true? 6 A. What I do know is that he is 7 not a toxicologist. 8 Q. Do you know what his area of 9 expertise is? 10 A. He's -- OB/GYN and oncology. 11 Q. Do you know what his level 12 of knowledge is in the area of 13 toxicology? 14 A. I do not. 15 Q. Have you ever met him? 16 A. Yes, I have met him. 17 Q. Have you ever talked to him 18 about his qualifications in the area of 19 toxicology? 20 A. No, I have not. But I know 21 he is not a -- he is not considered a 22 toxicologist by his peers, by colleagues. 23 He is known as a cancer oncologist. He 24 is not known or recognized as a</p>	<p style="text-align: right;">Page 556</p> <p>1 Q. Are you a board-certified 2 oncologist? 3 A. I am not, never claimed to 4 be. 5 Q. Are you a board-certified 6 gynecologic oncologist? 7 MS. O'DELL: Wait a minute. 8 THE WITNESS: I am not, nor 9 have I ever claimed to be. 10 Because -- 11 BY MR. HEGARTY: 12 Q. You were asked -- you were 13 asked about whether you could do -- 14 whether there could be studies looking at 15 risk of cancer in women exposed to 16 cobalt, chromium, and nickel. Do you 17 recall those questions? 18 A. I do. 19 Q. Studies looking at exposures 20 of metals in humans are done all the 21 time. They are called retrospective 22 case-control studies, correct? 23 A. They are not done in a 24 laboratory nor is there insertion of</p>
<p style="text-align: right;">Page 555</p> <p>1 toxicologist. 2 Q. Who have you ever asked -- 3 who have you ever spoken with regarding 4 to Dr. Neel's qualifications as it 5 relates to toxicology? 6 A. I have not spoken to him 7 about his qualifications. My answer 8 comes from the fact that I am an active 9 member in the Society of Toxicology, but 10 nationwide and internationally. And also 11 I'm an active member in the International 12 Union of Toxicology and active member in 13 the other -- other toxicology programs 14 and societies. 15 And I have -- I have not 16 seen Dr. Neel at any of these, nor have I 17 heard of him being spoken at or about in 18 these -- in these meetings. 19 Q. Do you go to OB/GYN 20 conferences? 21 A. I do not. 22 Q. Do you go to oncology 23 conferences? 24 A. I do not.</p>	<p style="text-align: right;">Page 557</p> <p>1 those metals into humans. 2 Q. That's not my question. You 3 said -- you testified that there is no 4 way that you can do a study looking at 5 the effect of nickel in humans. That's 6 not true, is it? 7 MS. O'DELL: Objection to 8 form. Misstates -- 9 THE WITNESS: I'm sorry. 10 MS. O'DELL: -- the question 11 and the testimony. 12 Excuse me, Doctor. 13 THE WITNESS: I was -- I was 14 talking about clinical studies and 15 studies in people. 16 BY MR. HEGARTY: 17 Q. There are retrospective 18 case-control studies looking at exposure 19 of humans to nickel, correct? 20 A. That is -- those are 21 epidemiological studies. My 22 understanding of the question that was 23 asked of me had to do with laboratory 24 studies and intentional exposure.</p>

<p style="text-align: right;">Page 558</p> <p>1 Q. Well, can you cite for me 2 any epidemiologic studies showing an 3 increased risk of ovarian cancer in women 4 exposed to nickel? 5 A. Nickel alone, I have not 6 reviewed that. But I do know the IARC 7 document talks about it as a Class 1 8 carcinogen. 9 Q. Can you cite for me, any 10 retrospective case-control studies, 11 showing an increased risk of ovarian 12 cancer in women exposed to chromium? 13 A. Chromium alone? 14 Q. Yes. 15 A. No, I cannot. 16 Q. Same question as to cobalt? 17 A. No, I cannot. 18 Q. Can you cite for me any 19 case-control studies looking at whether 20 there's an increased risk of ovarian 21 cancer in women exposed to nickel, 22 chromium, and cobalt in combination? 23 A. I hope I understand your 24 question right. But what I am -- what</p>	<p style="text-align: right;">Page 560</p> <p>1 is not unethical, but to use it in 2 a clinical study would be 3 extremely unethical. 4 BY MR. HEGARTY: 5 Q. It would also be appropriate 6 to do cell studies looking at nickel, 7 cobalt, and chromium in ovarian cancer 8 cells, correct? 9 MS. O'DELL: Objection to 10 form. 11 THE WITNESS: Alone -- I'm 12 sorry. Alone or in combination? 13 BY MR. HEGARTY: 14 Q. Or all of the above. 15 A. Your question was it would 16 be unethical to do cell culture studies? 17 Q. Would it be unethical in 18 your opinion? 19 A. Not to do cell culture 20 studies. 21 Q. Have such studies been done? 22 A. I'm not sure about the 23 combination. There have been studies, a 24 number of studies that have been done in</p>
<p style="text-align: right;">Page 559</p> <p>1 I'm saying is yes, there is an increased 2 risk in exposure to talc because talc 3 contains, according to the J&J documents, 4 and according to other studies that just 5 looked at talcum powder products, 6 contains nickel, cobalt, and chromium in 7 elevated levels. 8 Q. My question is specific to 9 looking only at exposure to cobalt, 10 nickel, and chromium. Can you cite for 11 me any case-control studies showing an 12 increased risk of ovarian cancer in women 13 exposed to those three metals in 14 combination? 15 A. No, I can't. 16 MS. O'DELL: Objection. 17 Asked and answered. 18 BY MR. HEGARTY: 19 Q. It would not be unethical to 20 do such a case-control study, correct? 21 MS. O'DELL: Objection. 22 THE WITNESS: A case-control 23 study or an epidemiological study 24 which uses data from populations</p>	<p style="text-align: right;">Page 561</p> <p>1 cell culture. I can't cite them all, 2 because there are numerous that have 3 looked at nickel or cobalt or chromium in 4 cell culture studies, and many that have 5 been done in my own laboratory. 6 Q. Can you cite to me any such 7 studies that have done those tests in 8 ovarian cells? 9 A. I'm sorry. When you say 10 "any such studies," do you mean cell 11 culture studies? 12 Q. Yes. 13 A. Well, the Shukla study, the 14 Saed studies. 15 Q. So the Shukla and Saed 16 studies applied nickel, chromium and 17 cobalt to the cells? 18 A. I'm sorry. I'm sorry. I 19 thought you said talcum powder. 20 Q. Doctor, listen to my 21 question. My question is can, you cite 22 for me any culture studies that have 23 applied nickel, cobalt, or chromium or 24 all three to ovarian cancer cells?</p>

<p style="text-align: right;">Page 562</p> <p>1 A. I cannot -- I have not seen 2 that literature, no. 3 Q. Those studies could be done, 4 correct? 5 A. Those studies could be done. 6 Q. They could be done in your 7 laboratory, couldn't they? 8 A. I have the facilities to 9 carry out those studies. 10 Q. You have not done those 11 studies? 12 MS. O'DELL: Objection to 13 form. 14 THE WITNESS: Correct. 15 BY MR. HEGARTY: 16 Q. You cited to the Cramer 2007 17 study, which I'm marking as Exhibit 18 Number 40. 19 (Whereupon, a discussion was 20 held off the stenographic record.) 21 (Document marked for 22 identification as Exhibit 23 Zelikoff-50.) 24 BY MR. HEGARTY:</p>	<p style="text-align: right;">Page 564</p> <p>1 of the first page on the right-hand 2 column. 3 A. Yes. 4 Q. The authors state that 5 the -- "First, the association is a 6 relatively weak" -- "a relatively weak 7 one; i.e., summary relative risk of 8 approximately 1.3." 9 Do you agree with that 10 statement? 11 MS. O'DELL: Objection to 12 form. 13 THE WITNESS: Number one, I 14 am not an epidemiologist so I'm 15 not testifying to epidemiological 16 odds ratio, whether that is weak 17 or not weak. 18 BY MR. HEGARTY: 19 Q. The next sentence says, 20 "Second, no clear increase in risk or 21 duration of use has been found in most 22 studies." 23 Do you agree with that 24 sentence?</p>
<p style="text-align: right;">Page 563</p> <p>1 Q. I'm marking as Exhibit 2 Number 50 the Cramer 2007 study that you 3 referred to in response to counsel's 4 questions. 5 A. Mm-hmm-hmm. 6 MS. O'DELL: Objection. 7 That misstates the record. I 8 never referred to the Cramer 9 study. 10 MR. HEGARTY: She cited it 11 in response to your questions. 12 MS. O'DELL: No, she did 13 not. But you may ask questions 14 about it, but that's not a proper. 15 MR. HEGARTY: Well, she 16 cited the Cramer 2007 article. 17 BY MR. HEGARTY: 18 Q. Do you find this article to 19 be a credible source of information for 20 you? 21 A. It was published in 22 Obstetrics and Gynecology. That is good 23 journal, reputable journal. 24 Q. And if you look at the top</p>	<p style="text-align: right;">Page 565</p> <p>1 MS. O'DELL: Objection to 2 form. 3 THE WITNESS: There are many 4 studies that do show that duration 5 plays a role. 6 BY MR. HEGARTY: 7 Q. That's not my question. My 8 question is do you agree with that 9 sentence? 10 A. I see. 11 MS. O'DELL: Objection to 12 form. Asked and answered. 13 THE WITNESS: I do not agree 14 that there is no clear -- there is 15 some evidence that leads to an 16 increase in risk associated with 17 duration of use. 18 BY MR. HEGARTY: 19 Q. So you don't agree with that 20 sentence? 21 A. So I do not completely agree 22 with that sentence. 23 Q. The next sentence reads, 24 "Third, the ability of talc used in the</p>

<p style="text-align: right;">Page 566</p> <p>1 genital area to enter the pelvic cavity 2 has not been conclusively proven." 3 Do you agree with that 4 sentence? 5 A. None of these are -- none of 6 these sentences are cited or referenced 7 by the way. 8 It has not been conclusively 9 proven. I agree with the sentence. 10 May I -- 11 Q. You cited as well to the 12 Keskin paper. You cited that several 13 times, including in response to counsel's 14 questions. 15 A. Yes, I did. I recall that. 16 Q. The Keskin paper was an 17 animal study that did not show tumor 18 formation from application of talc, 19 correct? 20 MS. O'DELL: Object to the 21 form. 22 THE WITNESS: If you allow 23 me to specifically look for that, 24 please.</p>	<p style="text-align: right;">Page 568</p> <p>1 findings that led to inflammation 2 including an increased number of 3 follicles, and that goes to 4 biological plausibility. 5 BY MR. HEGARTY: 6 Q. Did you agree with that 7 finding? 8 A. That there were increased 9 number of follicles? 10 Q. Yes. 11 A. And the histopathology? 12 That there was foreign body 13 reactions and that there were infections, 14 I agree with those studies. 15 Q. Do you agree with the 16 statement that the author made that this 17 effect seems to be in the form of foreign 18 body reaction or infection rather than a 19 neoplastic change? 20 A. I'm sorry, could you tell me 21 where that might be? 22 Q. Again, in the conclusion 23 section that we have just been looking 24 at.</p>
<p style="text-align: right;">Page 567</p> <p>1 BY MR. HEGARTY: 2 Q. I'll mark it as Exhibit 51. 3 (Document marked for 4 identification as Exhibit 5 Zelikoff-51.) 6 BY MR. HEGARTY: 7 Q. The Keskin paper over in the 8 conclusion section on Page 927 says that 9 with regard to the reported effects of 10 talc, "This effect seems to be in the 11 form of foreign body reaction or 12 infection rather than a neoplastic 13 change." 14 A. Which is inflammation. 15 Q. And in this study it showed 16 no neoplastic changes in any of the 17 animal study, correct? 18 MS. O'DELL: Object to the 19 form. 20 You may answer. 21 THE WITNESS: It was -- he 22 did not find or they did not find 23 that there was neoplastic changes, 24 but they did find a number of</p>	<p style="text-align: right;">Page 569</p> <p>1 A. Mm-hmm-hmm. 2 Well, a foreign body 3 reaction can -- is an immunological 4 response. Whether it's considered a 5 neoplastic change, likely not. A foreign 6 body reaction does not necessarily -- is 7 not necessarily known as a neoplastic 8 response, correct. 9 Q. And you -- you didn't cite 10 that statement from the Keskin paper in 11 your report, did you? 12 A. Not that I recall. 13 Q. Do you agree with the -- 14 A. But my -- my role was to 15 define biological plausibility. So what 16 I did -- what I did put in my report were 17 the things that indicated to me that 18 there was inflammation. 19 Q. You agree with the 20 conclusions from the Taher paper? 21 MS. O'DELL: Object to the 22 form. 23 Doctor, it's in this stack. 24 THE WITNESS: Okay. Thank</p>

<p style="text-align: right;">Page 570</p> <p>1 you. Oh, thank you.</p> <p>2 BY MR. HEGARTY:</p> <p>3 Q. Second page, Line 34, on the</p> <p>4 second page.</p> <p>5 A. In the abstract?</p> <p>6 Q. Yes.</p> <p>7 MS. O'DELL: Give me just a</p> <p>8 moment, I'm sorry. I'll pull out</p> <p>9 my copy.</p> <p>10 THE WITNESS: I'm sorry,</p> <p>11 should I wait?</p> <p>12 MR. HEGARTY: I think Leigh</p> <p>13 wants you to wait.</p> <p>14 MS. O'DELL: Okay. Go</p> <p>15 ahead. I'm sorry.</p> <p>16 BY MR. HEGARTY:</p> <p>17 Q. Do you agree with the</p> <p>18 statement made in Line 34?</p> <p>19 A. Perineal use of talc powder</p> <p>20 is a possible cause of human ovarian</p> <p>21 cancer?</p> <p>22 Q. Yes.</p> <p>23 A. I believe that it's more</p> <p>24 than a possible cause. I believe that</p>	<p style="text-align: right;">Page 572</p> <p>1 counsel has it. I'll hand it to you. If</p> <p>2 you'll --</p> <p>3 A. Oh. You mean the draft</p> <p>4 screening assessment?</p> <p>5 Q. Yes. Sorry, I was going to</p> <p>6 it by the wrong name. It is Exhibit --</p> <p>7 A. 9.</p> <p>8 Q. Thank you.</p> <p>9 If you'll turn to Page 16.</p> <p>10 A. I see that, Keskin et al.,</p> <p>11 2009, it's the first statement under</p> <p>12 human studies.</p> <p>13 Q. Yes. Right above that when</p> <p>14 it refers to the Keskin and colleagues</p> <p>15 2009. What was the conclusion that the</p> <p>16 sentence beginning "while no cancer"? Do</p> <p>17 you see that above human studies on</p> <p>18 Page 16?</p> <p>19 A. The conclusion, "while no</p> <p>20 cancer"?</p> <p>21 Q. Yes.</p> <p>22 A. "While no cancer/precancer</p> <p>23 effects were observed, Keskin and</p> <p>24 colleagues noted the study's duration may</p>
<p style="text-align: right;">Page 571</p> <p>1 there's biological plausibility which</p> <p>2 shows that it -- it could be, it is</p> <p>3 linked to human ovarian cancer.</p> <p>4 Q. So you don't -- you disagree</p> <p>5 with that statement?</p> <p>6 A. One could say that, taking</p> <p>7 it literally, that it is certainly a</p> <p>8 possible cause. I just believe that it</p> <p>9 is greater than a possible cause.</p> <p>10 MR. HEGARTY: Okay. Thank</p> <p>11 you. I think that's it for my</p> <p>12 time.</p> <p>13 MS. O'DELL: Okay.</p> <p>14 - - -</p> <p>15 EXAMINATION</p> <p>16 - - -</p> <p>17 BY MS. O'DELL:</p> <p>18 Q. Doctor, I just have two</p> <p>19 questions for you.</p> <p>20 I think you had the causal</p> <p>21 assessment in front of you.</p> <p>22 A. Do you mean the Taher?</p> <p>23 Q. No, ma'am. The actual</p> <p>24 causal assessment -- actually I think</p>	<p style="text-align: right;">Page 573</p> <p>1 have been too short to note these types</p> <p>2 of effects."</p> <p>3 Q. And in regard to -- and</p> <p>4 that -- that statement's consistent with</p> <p>5 the statements that you've included in</p> <p>6 your report, fair?</p> <p>7 MR. HEGARTY: Objection to</p> <p>8 form.</p> <p>9 THE WITNESS: Yeah.</p> <p>10 BY MS. O'DELL:</p> <p>11 Q. And then secondly you were</p> <p>12 asked a question, several questions about</p> <p>13 the actual Keskin paper itself. And I</p> <p>14 think it's still in front of you. Do you</p> <p>15 see that? It's Exhibit 51. Yeah,</p> <p>16 Exhibit 51.</p> <p>17 A. This is it, thank you.</p> <p>18 Q. Okay. And I'll turn you to</p> <p>19 the conclusion please, Dr. Zelikoff.</p> <p>20 A. That is on Page 930?</p> <p>21 Q. It's 927 actually. One of</p> <p>22 the conclusions, at least the ones I -- I</p> <p>23 was looking at.</p> <p>24 927. Do you see that?</p>

<p style="text-align: right;">Page 574</p> <p>1 A. I see.</p> <p>2 Q. And counsel directed your</p> <p>3 attention to the sentence that said,</p> <p>4 "However this effect seems to be in the</p> <p>5 form of foreign body reaction or</p> <p>6 infection rather than neoplastic change."</p> <p>7 Do you see that? Recall</p> <p>8 those questions --</p> <p>9 A. In the conclusion section?</p> <p>10 Q. Yes.</p> <p>11 A. On Page --</p> <p>12 Q. 927.</p> <p>13 A. "However this effect seems</p> <p>14 to be in the form of a foreign body</p> <p>15 reaction or infection rather than a</p> <p>16 neoplastic change."</p> <p>17 Yes, I see that.</p> <p>18 Q. And if you'll look to the</p> <p>19 next sentence, what also did the authors</p> <p>20 conclude?</p> <p>21 A. "Results of previous studies</p> <p>22 are in favor of a neoplastic effect,</p> <p>23 particularly in the ovaries."</p> <p>24 And they conclude that more</p>	<p style="text-align: right;">Page 576</p> <p>1 dissolved in DMSO.</p> <p>2 Q. Is -- is the data included</p> <p>3 in this manuscript, was that part of</p> <p>4 the -- the data you relied on in abstract</p> <p>5 in reaching your opinions in this case?</p> <p>6 A. In abstract form, yes. That</p> <p>7 was all that was -- that was available</p> <p>8 since this only came out a few weeks ago.</p> <p>9 MS. O'DELL: Okay. I have</p> <p>10 nothing further.</p> <p>11 THE WITNESS: Accepted for</p> <p>12 E-press a few weeks ago.</p> <p>13 MS. O'DELL: Okay. I have</p> <p>14 nothing further.</p> <p>15 - - -</p> <p>16 EXAMINATION</p> <p>17 - - -</p> <p>18 BY MR. HEGARTY:</p> <p>19 Q. Dr. Zelikoff, in looking at</p> <p>20 the Keskin paper, in -- in particular at</p> <p>21 the portion of the conclusions section</p> <p>22 that counsel asked you to read --</p> <p>23 A. Yes.</p> <p>24 Q. -- the results of previous</p>
<p style="text-align: right;">Page 575</p> <p>1 experimental and clinical studies are</p> <p>2 warranted.</p> <p>3 Q. All right. And one other</p> <p>4 question. You were asked about the Saed</p> <p>5 studies regarding talc and cell culture,</p> <p>6 both ovarian cancer cells and regular</p> <p>7 cells.</p> <p>8 A. Yes. I recall.</p> <p>9 Q. And you were asked earlier</p> <p>10 about the manuscript that's been marked</p> <p>11 as --</p> <p>12 A. Exhibit 8.</p> <p>13 Q. -- Exhibit 8.</p> <p>14 Is it -- is it -- turn to</p> <p>15 Page 5 of the manuscript please.</p> <p>16 A. I see it.</p> <p>17 Q. And looking at the top, did</p> <p>18 Dr. Saed use Johnson's Baby Powder as a</p> <p>19 part of the -- his treatment of cells?</p> <p>20 A. Yes. It's Page 5, top,</p> <p>21 treatment of cells, talcum powder from</p> <p>22 Fisher -- Fisher Scientific or Baby</p> <p>23 Powder from Johnson & Johnson, and the</p> <p>24 numbers of the lots are given were</p>	<p style="text-align: right;">Page 577</p> <p>1 studies, that sentence?</p> <p>2 A. Yes, I see it on Page 927.</p> <p>3 Q. Can you cite for me any</p> <p>4 previous studies to Keskin which were in</p> <p>5 favor of a neoplastic effect?</p> <p>6 A. Culture cell studies that</p> <p>7 have looked at proliferation, increased</p> <p>8 proliferation which was seen in the Saed</p> <p>9 studies and in the abstract.</p> <p>10 Proliferation is one hallmark of the</p> <p>11 carcinogenic process.</p> <p>12 Q. Doctor, listen to my</p> <p>13 question. This publication was in 2008.</p> <p>14 A. Okay. I'm sorry.</p> <p>15 MS. O'DELL: 2009 I believe,</p> <p>16 but go ahead.</p> <p>17 THE WITNESS: 2009.</p> <p>18 BY MR. HEGARTY:</p> <p>19 Q. Received December 2009.</p> <p>20 Published 2009.</p> <p>21 The sentence reads: The</p> <p>22 results of previous studies before 2009</p> <p>23 are in favor of neoplastic effect.</p> <p>24 What studies are they</p>

<p style="text-align: right;">Page 578</p> <p>1 referring to?</p> <p>2 A. I don't know because it's</p> <p>3 not referenced.</p> <p>4 MR. HEGARTY: I don't have</p> <p>5 any additional questions.</p> <p>6 MS. O'DELL: Nothing</p> <p>7 further, Doctor.</p> <p>8 THE VIDEOGRAPHER: Stand by</p> <p>9 please. This marks the end of</p> <p>10 today's deposition. The time is</p> <p>11 9:03 p.m. Off the record.</p> <p>12 (Excused.)</p> <p>13 (Deposition concluded at</p> <p>14 approximately 9:03 p.m.)</p> <p>15</p> <p>16</p> <p>17</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p>	<p style="text-align: right;">Page 580</p> <p>1 INSTRUCTIONS TO WITNESS</p> <p>2</p> <p>3 Please read your deposition</p> <p>4 over carefully and make any necessary</p> <p>5 corrections. You should state the reason</p> <p>6 in the appropriate space on the errata</p> <p>7 sheet for any corrections that are made.</p> <p>8 After doing so, please sign</p> <p>9 the errata sheet and date it.</p> <p>10 You are signing same subject</p> <p>11 to the changes you have noted on the</p> <p>12 errata sheet, which will be attached to</p> <p>13 your deposition.</p> <p>14 It is imperative that you</p> <p>15 return the original errata sheet to the</p> <p>16 deposing attorney within thirty (30) days</p> <p>17 of receipt of the deposition transcript</p> <p>18 by you. If you fail to do so, the</p> <p>19 deposition transcript may be deemed to be</p> <p>20 accurate and may be used in court.</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p>
<p style="text-align: right;">Page 579</p> <p>1</p> <p>2 CERTIFICATE</p> <p>3</p> <p>4</p> <p>5 I HEREBY CERTIFY that the</p> <p>6 witness was duly sworn by me and that the</p> <p>7 deposition is a true record of the</p> <p>8 testimony given by the witness.</p> <p>9</p> <p>10 It was requested before</p> <p>11 completion of the deposition that the</p> <p>12 witness, JUDITH ZELIKOFF Ph.D., have the</p> <p>13 opportunity to read and sign the</p> <p>14 deposition transcript.</p> <p>15</p> <p>16</p> <p>17</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p> <p>MICHELLE L. GRAY, A Registered Professional Reporter, Certified Shorthand Reporter, Certified Realtime Reporter and Notary Public Dated: January 23, 2019</p> <p>(The foregoing certification of this transcript does not apply to any reproduction of the same by any means, unless under the direct control and/or supervision of the certifying reporter.)</p>	<p style="text-align: right;">Page 581</p> <p>1 - - - - -</p> <p>2 E R R A T A</p> <p>3 - - - - -</p> <p>4 PAGE LINE CHANGE</p> <p>5</p> <p>6 REASON: _____</p> <p>7</p> <p>8 REASON: _____</p> <p>9</p> <p>10 REASON: _____</p> <p>11</p> <p>12 REASON: _____</p> <p>13</p> <p>14 REASON: _____</p> <p>15</p> <p>16 REASON: _____</p> <p>17</p> <p>18 REASON: _____</p> <p>19</p> <p>20 REASON: _____</p> <p>21</p> <p>22 REASON: _____</p> <p>23</p> <p>24 REASON: _____</p>

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ACKNOWLEDGMENT OF DEPONENT

I, _____, do
hereby certify that I have read the
foregoing pages, 1 - 583, and that the
same is a correct transcription of the
answers given by me to the questions
therein propounded, except for the
corrections or changes in form or
substance, if any, noted in the attached
Errata Sheet.

JUDITH ZELIKOFF Ph.D. DATE

Subscribed and sworn
to before me this

____ day of _____, 20____.

My commission expires: _____

Notary Public

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LAWYER'S NOTES

PAGE LINE

1	_____	_____	_____
2	_____	_____	_____
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Exhibit 22

TOXICOLOGICAL PROFILE FOR NICKEL

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

August 2005

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO NICKEL IN THE UNITED STATES

Nickel is a very hard metal that occurs naturally in soils and volcanic dust. Nickel is used in combination with other metals to form alloys used for coins, jewelry, and stainless steel. Nickel compounds are used for electroplating, to color ceramics, and in battery production.

Nickel is released to the atmosphere by windblown dust, volcanoes, combustion of fuel oil, municipal incineration, and industries involved in nickel refining, steel production, and other nickel alloy production. The form of nickel emitted to the atmosphere is dependent upon the source. Complex nickel oxides, nickel sulfate, and metallic nickel are associated with combustion, incineration, and smelting and refining processes. Ambient air concentrations of nickel range between 7 and 12 ng/m³, mainly in the form of aerosols and can be as high as 150 ng/m³ near point sources. Based on 1996 air quality data, EPA has reported average U.S. ambient air levels of 2.2 ng/m³. Ambient air levels of nickel are expected to be higher in urban air than in rural air. Concentrations of nickel in indoor air are generally 10 ng/m³.

Background levels of nickel in soils vary widely depending on local geology and anthropogenic inputs, but concentrations typically range between 4 and 80 ppm. Some areas of the United States may contain natural levels as high as 5,000 ppm. Concentrations of nickel in household dust can be high and therefore pose an increased risk to young children who have greater contact with floors. Nickel concentrations in surface water and groundwater range between 3 and 10 µg/L. Nickel levels in drinking water in the United States generally range from 0.55 to 25 µg/L and average between 2 and 4.3 µg/L. Based on these average nickel concentrations and a reference water intake of 2 L/day, the estimated average intake of nickel from drinking water ranges from 4 to 8.6 µg/day. Elevated levels of nickel may exist as a result of the corrosion and leaching of nickel alloys used in valves and faucets. For the general population, the predominant route of exposure to nickel is through food intake. Nickel intake in the United States ranges between 69 and 162 µg/day for adults (>18 years of age). Based on these average water and food nickel levels, a daily dose of 0.001–0.0024 mg/kg/day can be estimated using a reference body weight of 70 kg. In children, mean daily nickel intakes of 9, 39, 82, and 99 µg/day have been determined for children aged 0–6 months, 7–12 months, 1–3 years, and 4–8 years, respectively. The mean daily dietary intakes of

2. RELEVANCE TO PUBLIC HEALTH

nickel in children aged 9–18 years (128–137 µg/day in males and 101–109 µg/day for females) are similar to the mean intakes determined in adults (>18 years of age).

A 70 kg reference man contains 10 mg of nickel, giving an average body concentration of 0.1 ppm. Reference values for nickel in healthy adults is 0.2 µg/L in serum and 1–3 µg/L in urine. A National Health and Nutritional Examination Survey II of hair found mean nickel levels of 0.39 ppm, with 10% of the population having levels >1.50 ppm.

About 20–35% of the inhaled nickel that is retained in the lungs is absorbed into the blood. Absorption of nickel following oral exposure has been shown to vary (3–40%) depending on whether the nickel was in drinking water or food, with greater absorption occurring with drinking water. Fasting individuals have also been shown to absorb more nickel from the gastrointestinal tract. Most of the absorbed nickel is excreted in the urine, regardless of the route of exposure.

Nickel does not bioaccumulate to a great extent in animals. There is evidence of uptake and accumulation in certain plants.

Nickel is an essential trace element in animals, although the functional importance of nickel has not been clearly demonstrated. It is considered essential based on reports of nickel deficiency in several animal species (e.g., rats, chicks, cows, goats). Nickel deficiency is manifested primarily in the liver; effects include abnormal cellular morphology, oxidative metabolism, and increases and decreases in lipid levels. Decreases in growth and hemoglobin concentration and impaired glucose metabolism have also been observed. The essentiality of nickel in humans has not been established, and nickel dietary recommendations have not been established for humans.

2.2 SUMMARY OF HEALTH EFFECTS

The general population can be exposed to nickel via inhalation, oral, and dermal routes of exposure. Based on occupational exposure studies, reports of allergic contact dermatitis, and animal exposure studies, the primary targets of toxicity appear to be the respiratory tract following inhalation exposure, the immune system following inhalation, oral, or dermal exposure, and possibly the reproductive system and the developing organism following oral exposure.

3. HEALTH EFFECTS

Oskarsson 1991). An *in vitro* study of rat hepatocytes found that the calcium channels are involved in nickel uptake by the liver (Funakoshi et al. 1997). At physiological levels, no tissue significantly accumulates orally administered nickel (Nielsen 1990).

Nickel that is absorbed is excreted primarily in the urine. In the urine, nickel is primarily associated with low molecular weight complexes that have free amino acids as indicated by the ninhydrin reaction (Sunderman and Oskarsson 1991). In humans nickel is also eliminated in hair, skin, milk, and sweat.

The physiological role of nickel in animals and humans has not yet been identified. The most likely roles are as cofactors in metalloenzymes or metalloproteins, or as a cofactor that facilitates the intestinal absorption of iron (Fe^{3+} ion) (Nielsen 1982). Support for a role of nickel in enzymes comes from the identification of nickel-containing enzymes in plants and microorganisms. The types of nickel-containing enzymes that have been identified are urease, hydrogenase, methylcoenzyme M reductase, and carbon monoxide dehydrogenase (Nielsen 1990). Nickel may also have a role in endocrine gland function as suggested by its effect on prolactin levels.

3.5.2 Mechanisms of Toxicity

The mechanism of adverse respiratory effects following lung exposure of rabbits to metallic nickel or nickel chloride has been examined (Johansson and Camner 1986; Johansson et al. 1980, 1981, 1983, 1987, 1988a, 1989). In these studies, an accumulation of macrophages and granular material (primarily phospholipids) in the alveoli and an increase in volume density of alveolar type II cells were observed. The type II cells contained large amounts of lamellar bodies. Similar results were found following exposure to metallic nickel and nickel chloride, indicating that nickel ions apparently had a direct effect on type II cells (Johansson and Camner 1986). At the end of 6 months, all of the rabbits had foci of pneumonia, indicating an increased susceptibility to infection (Johansson et al. 1981). This may have been a result of the decreased function of the alveolar macrophages.

The substitution of nickel for other essential elements may also contribute to the adverse effects of nickel. Nickel can replace magnesium in certain steps in the activation of complement (McCoy and Kenney 1992). For example, the replacement of nickel for magnesium can increase the formation of C3b, Bb enzyme by 40 times, which amplifies activation of the complement pathway. Nickel has also been shown to activate calcineurin, a phosphatase that binds zinc and iron, and is usually activated by manganese.

3. HEALTH EFFECTS

There is some evidence that nickel may have a role in the release of prolactin from the pituitary. *In vitro* studies have shown that nickel could directly inhibit the release of prolactin by the pituitary, and it has been suggested that nickel may be part of a prolactin inhibiting factor (LaBella et al. 1973). Intravenous exposure to nickel chloride has been shown to reduce serum levels of prolactin in male rats that were pretreated with chlorpromazine, which itself produces hyperprolactinemia (LaBella et al. 1973). The effect was not observed in rats that had not been pretreated with chlorpromazine. Nickel has also been shown to accumulate more in the pituitaries of pregnant rats than nonpregnant rats (Sunderman et al. 1978), suggesting that a toxicological effect through prolactin may only be manifested during maximum prolactin production. A subcutaneous injection study has also shown that nickel can change the quality of the milk produced, resulting in increased milk solids (42%) and lipids (110%), and decreased protein (29%) and lactose (61%) (Dostal et al. 1989). Because these changes were noted in comparison to pair-fed rats, they were not considered to be a result of changes in food intake.

The mechanism of nickel carcinogenicity has not been firmly established; it is likely that the carcinogenic effects result from a variety of mechanisms. The available evidence suggests that, mechanistically, nickel carcinogenicity is probably the result of genetic factors and/or direct (e.g., conformational changes) or indirect (e.g., generation of oxygen radicals) epigenetic factors. Additionally, certain nickel compounds promote cell proliferation, which would convert repairable DNA lesions into nonrepairable mutations. Nickel is considered to be genotoxic, but has a low mutagenic potential (Kasprzak et al. 2003b). The nickel-induced DNA damage has resulted in the formation of chromosomal aberrations (Conway and Costa 1989; Dhir et al. 1991; Larramendy et al. 1981; Lechner et al. 1984; Sen and Costa 1986b; Sen et al. 1987; Waksvcik and Boysen 1982) that could result in deletion of senescence or tumor suppressor genes. Nickel compounds have also been found to be weak inducers of sister chromatid exchanges (Andersen 1983; Arrouijal et al. 1992; Larramendy et al. 1981; Ohno et al. 1982; Saxholm et al. 1981; Wulf 1980).

Although nickel has a relatively weak affinity for DNA, it has a high affinity for chromatin proteins, particularly histones and protamines (Costa et al. 1994; Kasprzak et al. 2003b; Oller et al. 1997). The complexing of nickel ions with heterochromatin results in a number of alterations including condensation, DNA hypermethylation, gene silencing, and inhibition of histone acetylation. These alterations have been shown to disturb gene expression (Costa et al. 1994; Kasprzak et al. 2003b; Lee et al. 1995; Oller et al. 1997; Zoroddu et al. 2002). Methylation of DNA may result in critical genes becoming incorporated into heterochromatin where they can no longer be expressed (Costa 1995). Some of the alterations in gene expression may be mediated by activated transcription factors. Nickel has been shown to alter several

3. HEALTH EFFECTS

transcription factors including hypoxia-inducible transcription factor (HIF-1), activating transcription factor (ATF-1) involved in inactivation of thrombospondin-1, which suppresses angiogenesis, and NF- κ B transcription factor involved in the inducible expression of adhesion molecules (Kasprzak et al. 2003b). The strongest epigenetic effects on nickel have been associated with HIF-1. The HIF-1 transcription factor is involved in the regulation of hypoxia-inducible genes involved in cell transformation, tumor promotion, and progression, angiogenesis, altered metabolism, and apoptosis. HIF-1 α , one of the HIF-1 subunits, is over-expressed in both primary and metastatic tumors. It is induced in response to hypoxia and exposure to nickel (Li et al. 2004; Salnikow et al. 2000b). Both soluble and insoluble nickel compounds have also been shown to induce Cap43 (also called NDRG2) gene expression, which requires HIF-1 α activation (Costa et al. 2003; Li et al. 2004; Salnikow et al. 2000b). There is also evidence that nickel ions inhibit DNA repair (Hartwig et al. 1994). Nickel enhances the genotoxicity of ultraviolet light, x-rays, *cis*- and *trans*-platinum, and mitomycin C. *In vitro* studies in HeLa cells suggest that nickel inhibits the incision step in excision repair (Hartwig et al. 1994), while studies using Chinese hamster ovary cells suggest that nickel inhibits the ligation step of excision repair (Lee-Chen et al. 1994). The underlying mechanism of how nickel affects DNA repair is unclear. Sunderman and Barber (1988), Sunderman (1989b), and Hartwig et al. (1994) suggest that nickel ions may compete with zinc ions for binding to zinc-finger DNA binding proteins, resulting in structural changes in DNA that prevent repair enzymes from binding. Nickel may also directly interact with enzymes required for DNA repair (Hartwig et al. 1994).

The binding of nickel to the histone protein within heterochromatin could result in the generation of oxygen radicals. These oxygen radicals could subsequently induce damage bases, DNA strand breaks, and DNA protein crosslinks (Costa et al. 1994; Oller et al. 1997). The available evidence suggests that this mechanism would play a minor (if any) role in nickel carcinogenicity because the damage would be confined to heterochromatin regions of DNA, which lack active genes (Oller et al. 1997). However, nickel ions can complex with a number of cellular ligands including amino acids, peptides, and proteins resulting in the generation of oxygen radicals. The reactive oxygen species (ROS) generated could nonselectively damage DNA, possibly resulting in genetic changes in active genes (Kasprzak et al. 2003b; Oller et al. 1997).

3.5.3 Animal-to-Human Extrapolations

The available data on the toxicity of inhaled nickel provide strong evidence that the respiratory tract, in particular the lung, is the most sensitive target of nickel toxicity in humans and animals. There are

Exhibit 23

TOXICOLOGICAL PROFILE FOR CHROMIUM

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

September 2012

3.5.2 Mechanisms of Toxicity

The toxic potency of chromium is dependent on the oxidation state of the chromium atom, with chromium(VI) more potent than chromium(III). The mechanisms of chromium toxicity and carcinogenicity are very complex. They are mediated partly through reactive intermediates during intracellular reduction of chromium(VI) to chromium(III) and oxidative reactions, and partly mediated by chromium(III) which is the final product of intracellular chromium(VI) reduction and forms deleterious complexes with critical target macromolecules (Chen and Shi 2002; Costa 2003; Costa and Klein 2006a; Ding and Shi 2002; Jeejeebhoy 1999; Levina and Lay 2005; Liu and Shi 2001; O'Brien et al. 2003; Paustenbach et al. 2003; Salnikow and Zhitkovich 2008; Shrivastava et al. 2002; Yao et al. 2008; Zhitkovich 2005). Chromium(III) may form complexes with peptides, proteins, and DNA, resulting in DNA-protein crosslinks, DNA strand breaks, and alterations in cellular signaling pathways, which may contribute to toxicity and carcinogenicity of chromium compounds.

The greater toxic potency of chromium(VI) relative to chromium(III) most likely is related to two factors: (1) the higher redox potential of chromium(VI) (Levina and Lay 2005; Reddy and Chinthamreddy 1999); and (2) the greater ability of chromium(VI) to enter cells (Costa 2003). Differences in molecular structure contribute the greater cellular uptake of chromium(VI) compared to chromium(III) (Costa 2003; Costa and Klein 2006a). At physiological pH, chromium(VI) exists as the tetrahedral chromate anion, resembling the forms of other natural anions (e.g., sulfate and phosphate) which are permeable across nonselective membrane channels. Chromium(III), however, forms octahedral complexes and cannot easily enter through these channels. Therefore, the lower toxicity to chromium(III) may be due in part to lack of penetration through cell membranes. It follows that extracellular reduction of chromium(VI) to chromium(III) may result in a decreased penetration of chromium into cells, and therefore, a decreased toxicity.

The higher redox potential of chromium(VI) contributes to the higher toxic potency of chromium(VI) relative to chromium(III) (Levina and Lay 2005), because once it is taken into cells, chromium(VI) is rapidly reduced to chromium(III), with chromium(V) and chromium(IV) as intermediates. These reactions commonly involve intracellular species, such as ascorbate, glutathione, or amino acids (Aiyar et al. 1991; Blankenship et al. 1997; Capellmann et al. 1995; Hojo and Satomi 1991; Kim and Yurkow 1996; Lin et al. 1992; Liu et al. 1997b; Mao et al. 1995; Wiegand et al. 1984; Zhitkovich et al. 1996). Chromium(VI), chromium(V), and chromium(IV) have all been shown to be involved in Fenton-like oxidative cycling, generating oxygen radical species (Aiyar et al. 1991; Chen et al. 1997; Liu et al. 1997b;

3. HEALTH EFFECTS

Luo et al. 1996; Mao et al. 1995; Molyneux and Davies 1995; Tsou et al. 1996). It is believed that the formation of these radicals, which leads to oxidative stress, may be responsible for many of the deleterious effects of chromium on cells, including lipid peroxidation (Bagchi et al. 2002a; Hojo et al. 1999, 2000) and alterations in cellular communication, signaling pathways and cytoskeleton (Chen et al. 1997; Gao et al. 2002; Gunaratnam and Grant 2002, 2004; Kim and Yurkow 1996; Mikalsen 1990; O'Hara et al. 2007; Shumilla et al. 1998; Wang et al. 1996a; Xu et al. 1996; Yao et al. 2008; Ye et al. 1995). The chromium(VI)-induced oxidative stress resulting from the generation of reactive oxygen species has been shown in *in vitro* studies to result in the induction and inhibition of the transcription factors, NF- κ B and AP-1, activation of p53, activation of hypoxia-inducible factor 1 (HIF-1), cell-cycle arrest, and p53-dependent apoptosis (Yao et al. 2008). Cellular damage from exposure to various chromium compounds can be blocked by radical scavengers, further strengthening the hypothesis that oxygen radicals play a key role in chromium toxicity (Hojo et al. 2000; Luo et al. 1996; Tsou et al. 1996; Ueno et al. 1995a).

The products of metabolic reduction of chromium(VI) (free radicals and chromium(IV) and (V)) and the newly generated chromium(III) are thought to be in part responsible for the carcinogenic effects seen in human and animal studies. The interaction of free radicals, chromium(V), chromium(IV), and chromium(III) with DNA can result in structural DNA damage, functional damage, and other cellular effects (Levina and Lay 2005; Singh et al. 1998a). The types of chromium-induced structural damage include DNA strand breaks (Aiyar et al. 1991; Bagchi et al. 2002a; Bryant et al. 2006; Casadevall et al. 1999; Ha et al. 2004; Kuykendall et al. 1996; Manning et al. 1992; Messer et al. 2006; Pattison et al. 2001; Ueno et al. 1995a), DNA-protein crosslinks (Aiyar et al. 1991; Blankenship et al. 1997; Capellmann et al. 1995; Costa et al. 1996, 1997; Kuykendall et al. 1996; Lin et al. 1992; Manning et al. 1992; Mattagajasingh and Misra 1996; Miller et al. 1991; O'Brien et al. 2005; Quievryn et al. 2001; Zhitkovich et al. 1996), DNA-DNA interstrand crosslinks (Xu et al. 1996), chromium-DNA adducts, and chromosomal aberrations (Blankenship et al. 1997; Sugiyama et al. 1986a; Umeda and Nishimura 1979; Wise et al. 1993). Functional damage includes DNA polymerase arrest (Bridgewater et al. 1994a, 1994b, 1998), RNA polymerase arrest, mutagenesis, and altered gene expression. However, DNA double strand breaks may not be due to free radical formation, but due to the formation of chromium-DNA ternary adducts, which lead to repair errors and collapsed replication forks (Ha et al. 2004). Double strand breaks can also lead to alterations in cellular communication and effects on signaling pathways and cytoskeleton. In addition, results of recent studies in human lung cells suggest that chromosome instability is an important mechanism in the development of lung cancers; specifically, chromium-induced chromosome

3. HEALTH EFFECTS

instability appears to be mediated through centrosome and spindle assembly checkpoint bypass (Holmes et al. 2006; Wise et al. 2006a).

Location of particle deposition in the lung and extracellular dissolution of chromium(VI) compounds (e.g., solubility) are also important considerations regarding the mechanism of chromium(VI)-induced carcinogenesis. In chromate workers, analysis of bronchial tissues shows higher chromium concentrations in areas of bronchial bifurcation compared to other areas in the bronchi (Ishikawa et al. 1994a). Also, autopsy results show that some precancerous bronchial lesions originated at bronchial bifurcations (Ishikawa et al. 1994b). Solubility of chromium(VI) compounds may also play a role in carcinogenic potency, with extracellular dissolution of the chromium compound critical to activity (Wise et al. 2004). This hypothesis is supported by *in vitro* data suggesting that extracellular chromium ions are the proximate clastogen in Chinese hamster ovary cells (Wise et al. 2004).

Chromium(III) can also interact with DNA to form adducts/complexes and DNA-protein crosslinks that interfere with DNA replication and transcription, and can promote the expression of regulatory genes such as nuclear factor- κ B, or may inhibit regulatory genes such as GRP78 (Chen et al. 1997; Kim and Yurkow 1996; Manning et al. 1992; Mikalsen 1990; O'Hara et al. 2003; Shumilla et al. 1998; Wang et al. 1996a; Xu et al. 1996; Ye et al. 1995). Disruption of these pathways by other compounds has been implicated in carcinogenesis. The structural and functional damage can lead to growth arrest (Xu et al. 1996) and apoptosis (Carlisle et al. 2000; Singh et al. 1999). Numerous studies show that chromium can induce apoptosis (Asatiani et al. 2004; Bagchi et al. 2001; Carlisle et al. 2000; Flores and Perez 1999; Gambelunghe et al. 2006; Gunaratnam and Grant 2002, 2004; He et al. 2007; Manyoats et al. 2002; Petit et al. 2004; Russo et al. 2005; Vasant et al. 2003); although the mechanism by which chromium induces apoptosis is not fully understood, it is believed to involve oxidative stress and activation of the p-53 protein (Pulido and Parrish 2003; Singh et al. 1998a).

3.5.3 Animal-to-Human Extrapolations

Species-related differences in chromium pharmacokinetics have been demonstrated, both between rodent species and between rodents and humans. However, studies directly examining species differences have been limited. Human microsomal chromium(VI) reduction is different from the P450-mediated microsomal reduction in rodents; specifically, the human system is much less oxygen-sensitive, has a much greater affinity for chromate, and is apparently mediated by flavoproteins (Myers and Myers 1998; Pratt and Myers 1993). Tissue distributions of chromium were found to be different between rats and

Exhibit 24

TOXICOLOGICAL PROFILE FOR COBALT

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

April 2004

3. HEALTH EFFECTS

Following inhalation exposure, significant levels of cobalt are found in the lungs of exposed humans and animals (Barnes et al. 1976; Brune et al. 1980; Collier et al. 1991; Gerhardsson et al. 1984; Hewitt 1988; Hillerdal and Hartung 1983; Kreyling et al. 1986; Kyono et al. 1992; Patrick et al. 1989; Talbot and Morgan 1989; Teraoka 1981). Within the lung, physiologically insoluble cobalt particles tend to be located within macrophages within the bronchial wall or in the interstitium close to the terminal bronchioli (Brune et al. 1980).

Excretion. Following inhalation exposure, the rate of urinary excretion appears to correlate with the rate of translocation of cobalt from the lungs to the blood, and the rate of fecal clearance with the rate of mechanical clearance of cobalt from the lungs to the gastrointestinal tract (Andre et al. 1989; Bailey et al. 1989; Collier et al. 1989; Kerfoot 1975; Kreyling et al. 1986, 1989; Palmes et al. 1959; Patrick et al. 1989; Talbot and Morgan 1989). Likewise, the majority of absorbed cobalt following oral exposure is rapidly removed from the body by excretion in the urine, and to a lesser extent in the bile and feces, with fecal elimination being the primary method of excretion for physiologically insoluble cobalt compounds in both humans and animals (Andre et al. 1989; Bailey et al. 1989; Collier et al. 1989; Harp and Scoular 1952; Paley et al. 1958; Patrick et al. 1989; Smith et al. 1972; Sorbie et al. 1971; Talbot and Morgan 1989; Valberg et al. 1969). The primary route for excretion following dermal exposure is the urine (Lacy et al. 1996; Scansetti et al. 1994).

3.6.2 Mechanisms of Toxicity

Stable Cobalt. The exact mechanisms by which cobalt exerts its effects on cells are not completely understood. However, a number of potential mechanisms have been identified. Several studies have demonstrated that hard metal, a metal alloy with a tungsten carbide and cobalt matrix, is considerably more toxic than either cobalt or tungsten carbide alone. A mechanism by which hard metal may exert its effects has been proposed by a group of Belgian researchers (Lasfargues et al. 1995; Lison et al. 1995, 1996). In this proposed mechanism, tungsten carbide, which is a very good conductor of electrons, facilitates the oxidation of cobalt metal to ionic cobalt (presumably Co^{2+}) by transferring electrons from the cobalt atom to molecular oxygen adjacent to the tungsten carbide molecule. The result is an increased solubility of cobalt, relative to cobalt metal alone, and the generation of active oxygen species. The cobalt ions formed may be absorbed into the blood and transported throughout the body, where they may elicit effects by the above mechanisms. *In vitro* evidence for this mechanism includes the ability of hard

3. HEALTH EFFECTS

metal particles, but neither cobalt nor tungsten carbide alone, to generate substantial levels of oxidant species and cause significant lipid peroxidation (Lison et al. 1995; Zanetti and Fubini 1997). Hard metal particles have also been shown to increase the levels of inducible nitric oxide synthase (iNOS), a gene responsive to oxidant stress (Rengasamy et al. 1999).

Another potential mechanism for cobalt toxicity is through oxidant-based and free radical-based processes. Exposure to soluble cobalt increases indices of oxidative stress, including diminished levels of reduced glutathione, increased levels of oxidized glutathione, activation of the hexose monophosphate shunt, and free-radical-induced DNA damage (Hoet et al. 2002; Kasprzak et al. 1994; Lewis et al. 1991; Zhang et al. 1998a); hydrogen peroxide appears to be a necessary cofactor for cobalt-induced oxidative DNA damage (Ivancsits et al. 2002). Cobalt has been shown to generate oxygen radicals, including superoxide, both *in vitro* and *in vivo* (Kadiiska et al. 1989; Kawanishi et al. 1994; Moorhouse et al. 1985), through what may be a Fenton-type mechanism (Lloyd et al. 1997). *In vivo* exposure to cobalt in rats and guinea pigs resulted in increased lipid peroxidation in the liver (Christova et al. 2001, 2002; Sunderman and Zaharia 1988), as well as changes in reduced glutathione and hepatic levels of superoxide dismutase, catalase, heme oxygenase, and glutathione peroxidase (Christova et al. 2001, 2002). Exposure to cobalt results in accumulation in cardiac tissues, and is thought to stimulate carotid-body chemoreceptors, mimicking the action of hypoxia (Di Giulio et al. 1990, 1991; Hatori et al. 1993; Morelli et al. 1994). Cobalt administration to a neuroblastoma/glioma cell line resulted in an upregulation of opioid delta receptors, through a mechanism similar to that of hypoxia (Mayfield et al. 1994). Exposure to cobalt also elicits effects on a number of genes known to be sensitive to oxidant status, including hypoxia-inducible factor 1, erythropoietin, vascular endothelial growth factor, catalase, and monooxygenase enzymes (Bunn et al. 1998; Daghighian et al. 1999; Dalvi and Robbins 1978; Di Giulio et al. 1991; Goldberg et al. 1988, 1994; Ho and Bunn 1996; Hoet et al. 2002; Ladoux and Frelin 1994; Legrum et al. 1979; Semenza et al. 1994; Yasukochi et al. 1974), and may also lead, through these genes or other pathways, to the induction of apoptosis (Zou et al. 2001).

Soluble cobalt has also been shown to alter calcium influx into cells, functioning as a blocker of inorganic calcium channels (Henquin et al. 1983; Moger 1983; Yamatani et al. 1998). This mechanism has been linked to a reduction of steroidogenesis in isolated mouse Leydig cells (Moger 1983). Additionally, soluble cobalt has been shown to alter the inorganic calcium influx in liver cells after exposure to glucagon (Yamatani et al. 1998), and calcium influx into pancreatic β cells (Henquin et al. 1983) and

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isolated rat islets (Henquin and Lambert 1975). Cobalt may also affect neuromuscular transmission though antagonism with calcium (Weakly 1973).

Another potential mechanism of cobalt toxicity is relevant to cobalt cardiomyopathy. As mentioned previously, cobalt accumulated in the heart of beer drinkers. Microscopic analysis revealed fragmentation and degeneration of myofibers and aggregates of abnormal mitochondria (Ferrans et al. 1964). These mitochondrial changes are indicative of disturbances in energy production or utilization possibly related to cobalt effects on lipoic acid. Cobalt irreversibly chelates lipoic acids under aerobic conditions (Webb 1982). Lipoic acid is a required cofactor for oxidative decarboxylation of pyruvate to acetyl CoA and of α -ketoglutarate to succinate (Lehninger 1982). In the myocardium of rats treated with cobalt, oxidation of pyruvate or fatty acids is impaired (Wiberg 1968).

A number of investigators have reported that cobalt ions can result in increased damage to DNA when co-exposed with oxidants *in vitro*, such as UV radiation or H₂O₂ (De Boeck et al. 1998; Hartwig et al. 1991; Nackerdien et al. 1991). It is believed that cobalt acts by inhibition of DNA repair, particularly the incision and polymerization steps (Asmuß et al. 2000; Kasten et al. 1997), accomplishing this through interaction with zinc finger DNA repair proteins (Asmuß et al. 2000; Sarkar 1995).

Another potentially important mechanism by which cobalt may exert effects is through its effects on heme and heme-containing enzymes. Cobalt is thought to inhibit heme synthesis *in vivo* by acting upon at least two different sites in the biosynthetic pathway: synthesis of 5-aminolevulinate and conversion of 5-aminolevulinate into heme (de Matteis and Gibbs 1977). This inhibitory activity might result in the formation of cobalt protoporphyrin rather than heme (Sinclair et al. 1979). Cobalt treatment also stimulates heme oxidation in many organs, due to the induction of heme oxygenase (for review, see Sunderman 1987). Effects on heme synthesis may potentially affect a wide variety of heme-containing proteins, including monooxygenase enzymes (i.e., cytochromes P450) and catalase (Legrum et al. 1979; Yasukochi et al. 1974). Conversely, cobalt acts, through a mechanism believed to involve a heme-containing protein, to increase erythropoietin, which stimulates the production of red blood cells (Di Giulio et al. 1991; Goldberg et al. 1988; Smith and Fisher 1973). The regulatory mechanisms behind this apparent dichotomy have not been fully elucidated.

Another potential mechanism by which cobalt may exert its effects is through interactions with the immune system. Exposure of humans to cobalt by the inhalation and dermal routes have resulted in

3. HEALTH EFFECTS

sensitization to cobalt (Alomar et al. 1985; Bencko et al. 1983; Doods-Goossens et al. 1980; Fischer and Rystedt 1983; Goh et al. 1986; Kanerva et al. 1988; Marcussen 1963; Shirakawa et al. 1988, 1989; Valer et al. 1967). Exposure to inhaled cobalt chloride aerosols can precipitate an asthmatic attack in sensitized individuals (Shirakawa et al. 1989), suggesting cobalt sensitization as one mechanism by which cobalt-induced asthma may be produced. IgE and IgA antibodies specific to cobalt have been reported in humans (Bencko et al. 1983; Shirakawa et al. 1988, 1989). There is evidence that cobalt sensitivity in humans may be regulated by T-lymphocytes (Katsarou et al. 1997). A human helper T-lymphocyte cell line specific for cobalt (CoCl₂) has been established (Löfström and Wigzell 1986). Cobalt may also interact directly with immunologic proteins, such as antibodies or Fc receptors, to result in immunosensitization (Cirla 1994). *In vitro*, cobalt(II) has been shown to reduce the proliferation of both B and T lymphocytes, as well as the release of the cytokines IL-2, IL-6, and IFN-Gamma (Wang et al. 1996). Interrelationships exist between nickel and cobalt sensitization (Bencko et al. 1983; Rystedt and Fisher 1983); however, the extent of any potential interactions between the two metals on immunologic end points is not well understood. In guinea pigs, nickel and cobalt sensitization appear to be interrelated and mutually enhancing (Lammintausta et al. 1985), though cross-reactivity was not reported to occur.

Cobalt has been shown to have a number of effects on glucose metabolism. Treatment of animals with cobalt results in a depression of serum (Eaton and Pommer 1973; Ybarra et al. 1997) or tissue (Wiberg 1968) glucose levels. In rats made diabetic by pretreatment with streptozotocin, this depression was persistent, whereas it was transient in normal rats (Ybarra et al. 1997). Many of the effects of cobalt on glucose metabolism are thought to result from alterations in the expression of the glut family of glucose transport proteins, a family of facilitative Na⁺-independent transport proteins thought to mediate non-insulin-dependent transport of glucose. Exposure to soluble cobalt results in increased expression of these genes, particularly GLUT1, in cells of the liver, kidney cortex, myocardium, skeletal muscle, and cerebrum (Behrooz and Ismail-Beigi 1997; Ybarra et al. 1997). Cobalt also reduces the amount of glucose produced in liver cells following stimulation with glucagon (Eaton and Pommer 1973; Yamatani et al. 1998), as well as reducing insulin release in isolated rat islets (Henquin and Lambert 1975).

Radioactive Cobalt. Due to the nature of its ionizing radiation, radioactive cobalt can present a health hazard. Highly-penetrating gamma emissions are the major source of damage to tissues and internal organs following external exposure to radioactive cobalt isotopes. If radioactive cobalt is internalized, nearby tissues are at highest risk for damage due to the release of beta particles. In either case, exposure to ionizing radiation results in an increased risk of cellular damage. Both beta and gamma radiations are

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capable of producing ionization events when they hit cellular molecules, including DNA, RNA, or lipids. Ionized molecules within irradiated cells may be repaired quickly to prevent further damage. On the other hand, irreparable damage may be imposed on cellular materials, such as DNA, which might ultimately result in either cell death or the formation of cancerous tumors. Very large acute radiation doses can damage or kill enough cells to cause the disruption of organ systems, resulting in acute radiation syndrome or even death. Human and animal data indicate that sufficiently high exposures to cobalt radiation can result in adverse effects such as reduced fertility, abnormal development, genotoxicity, pulmonary fibrosis, gastrointestinal atrophy and fibrosis, hematological and lymphoreticular disorders, cancer, and death (Chang et al. 1999b; Davis et al. 1992; Dinehart et al. 1991; Hashimoto and Mitsuyasu 1967; Klener et al. 1986; Libshitz 1993; Myskowski and Safai 1981; Rauscher and Bauchinger 1983; Roschler and Woodard 1969; Roswit and White 1977; Stavem et al. 1985; Van Oort et al. 1984). For a more complete discussion of the mechanisms associated with the toxic effects of ionizing radiation, refer to Chapter 5 of the Toxicological Profile for Ionizing Radiation (Agency for Toxic Substances and Disease Registry 1999).

3.6.3 Animal-to-Human Extrapolations

Bailey et al. (1989) reported a wide variation across species, including man, in the retention and clearance of inhaled physiologically insoluble ⁵⁷Co particles (see Table 3-8), noting that this variation illustrates the potential difficulty of extrapolating the results of animal lung retention experiments to human even qualitatively. Species differences in absorption of physiologically insoluble cobalt oxide following oral exposure do not appear to exist (Bailey et al. 1989), although humans were not examined. Absorption of soluble cobalt compounds is greater in rats (13–34%) than in dairy cows (1–2%) and guinea pigs (4–5%) following oral exposure (Ayala-Fierro et al. 1999; Barnaby et al. 1968; Hollins and McCullough 1971; Kirchgessner et al. 1994; Naylor and Harrison 1995; Schade et al. 1970; Taylor 1962; van Bruwaene et al. 1984).

3.7 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as endocrine disruptors. However, appropriate

Exhibit 25

Chromium Hexavalent Compounds

CAS No. 18540-29-9

Known to be human carcinogens

First listed in the *First Annual Report on Carcinogens* (1980)

Carcinogenicity

Chromium hexavalent (VI) compounds are *known to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Epidemiological studies in various geographical locations have consistently reported increased risks of lung cancer among workers engaged in chromate production, chromate pigment production, and chromium plating. Epidemiological studies of lung cancer among ferrochromium workers were inconclusive. Exposure to specific chromium compounds varies by industry. Chromate-production workers are exposed to a variety of chromium compounds, including hexavalent (VI) and trivalent (III) compounds. Chromate-pigment workers are exposed to chromates in the pigment and to soluble chromium(VI) compounds used in pigment production. Chrome platers are exposed to soluble chromium(VI) compounds and possibly to nickel. Ferrochromium workers are exposed mainly to chromium(III) compounds and possibly to chromium(VI) compounds. Epidemiological studies of stainless-steel welders exposed to chromium(VI) compounds also found an increased risk of lung cancer; however, these studies are of limited use for evaluation of chromium's carcinogenicity, because the welders were also exposed to other potential carcinogens. In addition, epidemiological studies of chromate production workers, chromate pigment workers, and chrome platers found an increased risk of a rare cancer of the sinonasal cavity. The data for cancer at sites other than the lung and sinonasal cavity were unclear. The International Agency for Research on Cancer concluded that there was sufficient evidence in humans for the carcinogenicity of chromium(VI) compounds as encountered in the chromate-production, chromate-pigment-production, and chromium-plating industries (IARC 1973, 1979, 1990).

Cancer Studies in Experimental Animals

Exposure to chromium(VI) compounds (calcium chromate, chromium trioxide, or sodium dichromate) via inhalation or intratracheal or intrabronchial implantation caused benign and/or malignant lung tumors in rats and/or mice. Intrabronchial implantation of zinc chromate or strontium chromate also caused bronchial tumors in rats, and inhalation exposure to chromium trioxide caused benign nasal tumors in mice. In addition, cancer at the injection site was observed in rats following administration of chromium compounds (calcium chromate, lead chromate, basic lead chromate, zinc chromate, or strontium chromate) by intrapleural, subcutaneous, or intramuscular injection and in mice following intramuscular injection of calcium chromate (IARC 1980, 1990). IARC (1990) concluded that there was sufficient evidence in experimental animals for the carcinogenicity of calcium chromate, lead chromates, strontium chromate, and zinc chromates and limited evidence for the carcinogenicity of chromium trioxide and sodium dichromate.

Since chromium hexavalent compounds were reviewed for listing in the *First Annual Report on Carcinogens* and reviewed by IARC in 1990, the National Toxicology Program has conducted two-year cancer studies of sodium dichromate in rats and mice. Sodium dichromate administered in the drinking water caused cancer of the

oral cavity (squamous-cell carcinoma of the oral mucosa) in rats and increased the combined incidence of benign and malignant tumors (adenoma and carcinoma) of the small intestine (duodenum, jejunum, or ileum) in mice (NTP 2008).

Studies on Mechanisms of Carcinogenesis

Chromosomal aberrations, sister chromatid exchange, and aneuploidy were observed in workers exposed to chromium(VI) compounds. Chromium(VI) compounds also caused genetic damage in a variety of test systems. Most caused mutations and DNA damage in bacteria; however, the poorly soluble compounds had to be dissolved in acids or alkalis to produce genetic effects. A few compounds also caused mutations in yeast and insects. Many chromium(VI) compounds caused genetic damage in cultured human and other animal cells and in experimental animals exposed *in vivo*. The compounds tested included ammonium chromate and dichromate, calcium chromate, chromium trioxide, sodium chromate and dichromate, potassium chromate and dichromate, strontium chromate, and the industrial product basic zinc chromate (zinc yellow). Among the types of genetic damage observed were gene mutations (including dominant lethal mutations), DNA damage, sister chromatid exchange, chromosomal aberrations, and cell transformation (IARC 1990).

IARC (1990) concluded that there was sufficient evidence in humans for the carcinogenicity of chromium(VI) compounds based on the combined results of epidemiological studies, cancer studies in experimental animals, and evidence that chromium(VI) ions generated at critical sites in the target cells were responsible for the carcinogenic action observed.

Properties

Elemental chromium is a transition-group metal belonging to group VIB of the periodic table and has oxidation states ranging from -2 to $+6$, of which the divalent ($+2$, II), trivalent ($+3$, III), and hexavalent ($+6$, VI) forms are the most important. Elemental chromium does not occur naturally in the environment. The divalent (chromous) state is readily oxidized to the more stable trivalent (chromic) state. Although the hexavalent state (including chromates) is more stable than the divalent state, it is rarely found in nature. Chromium(VI) compounds are strong oxidizing agents and are highly corrosive. In the environment, they generally are reduced to chromium(III) compounds. The chromium(VI) compounds most commonly encountered in industry are calcium chromate, chromium trioxide, sodium chromate and dichromate, potassium chromate and dichromate, lead chromate, strontium chromate, and zinc chromate (IARC 1990, Costa 1997). However, this listing applies to all hexavalent chromium compounds, not just to those specified above.

Calcium chromate occurs as yellow crystals or a bright-yellow powder. It is slightly soluble in water and soluble in dilute acids, and it reacts with acids and ethanol. Although calcium chromate is not flammable, toxic chromium fumes may be formed in fires, and mixtures with boron burn violently when ignited. Chromium trioxide (also known as chromic trioxide) occurs as dark-red or brown crystals, flakes, or granular powder and is soluble in water, ethyl alcohol, ethyl ether, sulfuric acid, and nitric acid. Contact of chromium trioxide with organic chemicals may result in violent or explosive reactions, and fires with chromium trioxide may produce irritating, corrosive, and toxic gases (ATSDR 2000, HSDB 2009). Lead chromate occurs as yellow, orange, or red crystals or a yellow or orange-yellow powder that is insoluble in water, acetic acid, and ammonia but soluble in dilute nitric acid. When heated, it emits highly toxic fumes, and it may react explosively with azo dyes. The term "lead chromate" is also used to refer to various commercial lead chromate pigments (IARC

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1980, 1990, HSDB 2009). Potassium chromate occurs as yellow crystals and is soluble in water but insoluble in ethanol. Potassium dichromate occurs as red or orange-red crystals and is soluble in water but insoluble in ethanol and acetone. It poses a dangerous fire risk when in contact with organic materials or finely divided combustible materials, such as sawdust (ATSDR 2000, HSDB 2009).

Sodium chromate occurs as yellow crystals and is soluble in water and slightly soluble in methanol. Although it is not flammable, toxic chromium oxide fumes may be formed in fires with sodium chromate (ATSDR 2000, HSDB 2009). Sodium dichromate occurs as bright orange-red or red hygroscopic crystals and is soluble in water and methanol. It reacts explosively with hydrazine, acetic anhydride, boron, silicon, and other materials (IARC 1980, HSDB 2009). Strontium chromate occurs as yellow monoclinic crystals or a yellow powder. It is slightly soluble in water and soluble in dilute hydrochloric acid, nitric acid, and acetic acid. It is not flammable but reacts explosively with hydrazine (HSDB 2009). Zinc chromate occurs as lemon-yellow crystals or powder. It is insoluble in cold water and acetone, sparingly soluble in hot water, and soluble in acid and liquid ammonia. Zinc chromate reacts explosively with hydrazine. The term "zinc chromate" is also used to refer to various commercial zinc and zinc potassium chromates (IARC 1990, HSDB 2009). Physical and chemical properties of these chromium(VI) compounds are listed in the following table, along with their chemical formulas.

Use

The steel industry is the major consumer of chromium. In 2007, estimated consumption of chromium in the United States by end use was 78% in stainless and heat-resisting steel, 13.8% for other steel uses, 3.7% in superalloys, and 4.5% in other alloys and end uses (Papp 2009). Alloys of stainless steel and chromium typically contain between 11.5% and 30% chromium (ATSDR 2000). Chromium(VI) compounds are widely used as corrosion inhibitors, in the manufacture of pigments, in metal finishing and chrome plating, in stainless steel production, in leather tanning, and in wood preservatives (Costa 1997, ATSDR 2000). In 1996, about 52% of all chromium compounds used in the U.S. chemical industry were used in production of wood preservatives; the rest were used in leather tanning (13%), metals finishing (13%), pigments (12%), refractories (linings for high-temperature industrial furnaces) (3%), and other uses (7%) (ATSDR 2000). The use of chromium(VI) compounds in wood preservatives increased dramatically from the late 1970s to the early 2000s; however, this use is expected to decrease because of a voluntary phase-out of all residential uses of wood treated with chromated copper arsenate (pressure-treated wood) that went into effect December 31, 2003 (Brooks 2009). Chromium(VI) compounds are also used in textile-dyeing processes, printing inks, drilling muds, pyrotechnics, water treatment, and chemical synthesis (HSDB 2009).

Calcium chromate is used primarily as a corrosion inhibitor and as a depolarizer in batteries (IARC 1973, 1990, HSDB 2009). Chromium trioxide is used primarily in chrome plating and other metal

finishing (particularly in the production of automobiles and military aircraft), in production of wood preservatives, as a corrosion inhibitor, and in production of organic chemicals and catalysts. Lead chromate has been used in paints and printing inks and as a colorant in vinyl, rubber, and paper. Potassium chromate is used in production of dyes and in textile-dyeing processes. Potassium dichromate has largely been replaced by sodium dichromate in many applications; however, it is still used in photomechanical processes and production of pigments and wood preservatives. Sodium chromate is used as a corrosion inhibitor and in textile dyeing processes, inks, paints, leather tanning, wood preservatives, drilling muds, cutting oils, water treatment, and production of other chromium compounds. Sodium dichromate is the primary base material for the production of chromium compounds and is used as a corrosion inhibitor, in metal treatments, in drilling muds, and in the production of dyes, wood preservatives, synthetic organic chemicals, and catalysts. Strontium chromate is used as a corrosion inhibitor and metal conditioner, in aluminum flake coatings, as a colorant in polyvinyl chloride, in pyrotechnics, in chrome plating, and for sulfate ion control in electrochemical processes. Zinc chromates are used as corrosion inhibitors and metal conditioners and in paints, varnishes, and oil colors.

Production

The United States is one of the world's leading producers of chromium compounds. U.S. primary production levels of chromium (i.e., mine production of chromite ore) have not been reported since 1961 (USGS 2010). One surface mine was developed in the United States in the mid to late 2000s (Papp 2009, 2010), but production levels have not been reported. Other domestic sources of chromium include recycled stainless-steel scrap, industry stocks, and the Defense National Stockpile. In 2009, the U.S. chromium supply from recycled stainless-steel scrap was 160,000 metric tons (353 million pounds), down from an average of 174,000 metric tons (383 million pounds) from 2000 to 2008 (Papp 2010, USGS 2010). The supply from industry stocks was not reported for 2009; however, this source supplied an average of 10,200 metric tons (23 million pounds) from 2000 to 2008. The government stockpile releases in 2009 were 1,000 metric tons (2.2 million pounds), down from an average of 464,000 metric tons (1 billion pounds) from 2000 to 2008. In 2009, U.S. imports of chromium were 150,000 metric tons (331 million pounds), down from an average of 455,000 from 2000 to 2008, and exports were 50,000 metric tons (110 million pounds), down from an average of 181,000 metric tons (400,000 pounds) (Papp 2010). In 2009, apparent consumption of chromium was 260,000 metric tons (573 million pounds), down from average of 538,000 metric tons (1.2 billion pounds) from 2000 to 2008.

U.S. production of calcium chromate in 1977 was at least 5,450 kg (12,000 lb); no other production data and no U.S. import or export data were found. In the late 1970s and early 1980s, annual U.S. pro-

Compound	Formula	Molec. wt.	Density (g/cm ³) ^a	Melting pt.	Dec.
Calcium chromate	CaCrO ₄	156.1	2.89	NR	NR
Chromium trioxide	CrO ₃	100.0	2.70	197°C	yes
Lead chromate	PbCrO ₄	323.2	6.12	844°C	yes
Potassium chromate	K ₂ CrO ₄	194.2	2.73	975°C	NR
Potassium dichromate	K ₂ Cr ₂ O ₇	294.2	2.68	398°C	~500°C
Sodium chromate	Na ₂ CrO ₄	162.0	2.72	792°C	NR
Sodium dichromate	Na ₂ Cr ₂ O ₇	262.0	2.52	357°C	400°C
Strontium chromate	SrCrO ₄	203.6	3.90	NR	NR
Zinc chromate	ZnCrO ₄	181.4	3.40	NR	NR

Source: HSDB 2009. ^aSource specifies the temperature at which density was determined for some but not all of the compounds. Dec. = decomposes; NR = not reported.

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duction of chromium trioxide was around 30 million kilograms (66 million pounds). Annual production capacity was 52 million kilograms (115 million pounds) in 1988; no more recent data were found. Annual U.S. imports of chromium trioxide ranged from 200,000 kg (440,000 lb) in 1977 to 16.5 million kilograms (36.4 million pounds) in 2002; 2008 imports were 8.9 million kilograms (19.6 million pounds). U.S. exports of chromium trioxide were 4.1 million kilograms (9 million pounds) in 1977, 11.6 million kilograms (25.6 million pounds) in 2000, 8.4 million kilograms (18.5 million pounds) in 2002, and 17.4 million kilograms (38.4 million pounds) in 2008 (IARC 1990, HSDB 2009, USITC 2009).

In 1966, U.S. production of potassium chromate and dichromate combined was estimated at 2.6 million to 3.8 million kilograms (5.7 million to 8.4 million pounds). Production of potassium dichromate declined throughout the 1970s, from 3.2 million kilograms (7.1 million pounds) in 1972 to 1.0 million kilograms (2.2 million pounds) in 1978. No more recent production data for potassium chromate or dichromate were found. In the mid 1980s, combined annual U.S. imports of potassium chromate and dichromate ranged from 580,000 kg (1.3 million pounds) to 1.0 million kilograms (2.2 million pounds) (IARC 1990). U.S. imports of potassium dichromate were 189,000 kg (416,000 lb) in 2002 but only 5,000 kg (11,000 lb) in 2008, while U.S. exports decreased from 26,000 kg (57,000 lb) to 77,000 kg (170,000 lb) (USITC 2009).

The United States produced 139,000 short tons of sodium chromate and dichromate combined in 1998 and 140,700 short tons in 1999 (HSDB 2009). U.S. imports of sodium chromate and dichromate were 4.2 million kilograms (9.3 million pounds) in 1982. Imports of sodium dichromate only were 18.8 million kilograms (41.4 million pounds) in 2002 and 33 million kilograms (72.8 million pounds) in 2008. U.S. exports of sodium chromate and dichromate were 8.8 million kilograms (19.4 million pounds) in 1985 and 26.3 million kilograms (58 million pounds) in 1999. Exports of sodium dichromate only were 12.6 million kilograms (27.8 million pounds) in 2002 and 31.3 million kilograms (69 million pounds) in 2008 (HSDB 2009, USITC 2009).

The United States produced 680,000 kg (1.5 million pounds) of strontium chromate in 1970 (IARC 1990). No other production data were found. U.S. imports of strontium chromate were 300,000 kg (660,000 lb) in 1978, 250,000 kg (550,000 lb) in 1982, 180,000 kg (400,000 lb) in 1984, 390,000 kg (860,000 lb) in 1985, and 120,000 kg (265,000 lb) in 1986 and 1987 (IARC 1990, HSDB 2009). No data on U.S. exports were found. The United States produced 30.6 million kilograms (67 million pounds) of lead chromate in 1972 (HSDB 2009). In 1976 and 1977, 20 million kilograms (44 million pounds) of lead chromate were used annually to produce chrome yellow and chrome orange pigments (IARC 1990). No production data were found for zinc chromate. U.S. imports of lead and zinc chromate combined were 289,000 kg (638,000 lb) in 2000, 135,500 kg (300,000 lb) in 2002, and 8.9 million kilograms (19.6 million pounds) in 2008. U.S. exports were 287,500 kg (634,000 lb) in 2000 and 125,000 kg (275,000 lb) in 2002 (USITC 2009). In 2008, no lead or zinc chromate was imported or exported.

Exposure

Chromium, in the form of unidentified chromium compounds, occurs naturally in the earth's crust and is widely distributed in air, water, soil, and food. Chromium(III) is an essential trace element in humans. The general population is exposed to some chromium(VI) compounds, but the levels of exposure vary. Environmental exposure specifically to chromium(VI) compounds is difficult to quantify, because specific forms of chromium seldom are identified in exposure

studies. Although chromium(VI) compounds in the environment may be reduced to chromium(III) compounds, hexavalent forms can persist under some conditions. The general population may be exposed to chromium(VI) compounds through inhalation of ambient air, ingestion of water, or dermal contact with products that contain chromium(VI) compounds, such as pressure-treated wood. People who live near industrial facilities that use chromium(VI) compounds or near chromium waste disposal sites have the greatest potential for exposure (ATSDR 2000).

A 1990 study reported the average concentration of chromium(VI) to be 0.0012 $\mu\text{g}/\text{m}^3$ (range = < 0.001 to 3 $\mu\text{g}/\text{m}^3$) in indoor air samples collected from residences in Hudson County, New Jersey. Other reports of exposure to chromium were not specific for chromium(VI) compounds, but provide general information on exposure to chromium and chromium compounds. Between 1977 and 1984, typical total chromium concentrations in ambient air in the United States were less than 0.01 $\mu\text{g}/\text{m}^3$ in rural areas and 0.01 to 0.03 $\mu\text{g}/\text{m}^3$ in urban areas. Average atmospheric concentrations of chromium from more than 2,100 monitoring stations ranged from 0.005 to 0.525 $\mu\text{g}/\text{m}^3$. A survey of more than 3,800 tap water samples in 1974 and 1975 found chromium concentrations ranging from 0.4 to 8.0 $\mu\text{g}/\text{L}$, with a mean of 1.8 $\mu\text{g}/\text{L}$. In surveys of U.S. surface waters, chromium concentrations in rivers ranged from less than 1 to 30 $\mu\text{g}/\text{L}$, and concentrations in lakes typically were less than 5 $\mu\text{g}/\text{L}$. Typical chromium levels in most fresh foods are low; chromium was detected in vegetables, fruits, grains, cereals, eggs, meat, and fish at concentrations of between 20 and 520 $\mu\text{g}/\text{kg}$. The mean daily dietary intake of chromium was estimated to be less than 0.2 to 0.4 μg from air, 2.0 μg from water, and 60 μg from food (ATSDR 2000).

According to the U.S. Environmental Protection Agency's Toxics Release Inventory, environmental releases of chromium compounds since reporting began in 1988 were lowest in 2001 (about half the average from 1988 to 2000). In 2007, 1,384 facilities released 12 million pounds of chromium, and 1,147 facilities released 51 million pounds of chromium compounds. The 100 facilities with the largest releases accounted for most of the total amounts released (TRI 2008).

Most occupational exposure to chromium(VI) compounds is through inhalation or dermal contact. Exposure to specific chromium compounds varies by industry. Chromate production workers are exposed to a variety of chromium compounds, including chromium(VI) and chromium(III) compounds. Chromate pigment workers are exposed to chromates in the pigment and to soluble chromium(VI) compounds used in pigment production. Chrome platers are exposed to soluble chromium(VI) compounds and possibly to nickel. Ferrochromium workers are exposed mainly to chromium(III) compounds and possibly to chromium(VI) compounds.

Occupational exposure to chromium generally exceeds non-occupational exposure. However, concentrations of airborne chromium in workplaces have declined significantly since the 1980s because of improved emission controls. Typical concentration ranges for airborne chromium(VI) in industries that use chromium(VI) compounds are as follows: stainless-steel welding, 50 to 400 $\mu\text{g}/\text{m}^3$; chromate production, 100 to 500 $\mu\text{g}/\text{m}^3$; chrome plating, 5 to 25 $\mu\text{g}/\text{m}^3$; ferrochrome alloy production, 10 to 140 $\mu\text{g}/\text{m}^3$; and chromate pigment production, 60 to 600 $\mu\text{g}/\text{m}^3$ (IARC 1990, ATSDR 2000). In the tanning industry, hides are soaked with chromium(VI) compounds in the presence of other chemicals that reduce them to chromium(III) compounds (Costa 1997); therefore, exposure in the tanning industry is almost exclusively to soluble chromium(III) (ATSDR 2000). In a study assessing chromium exposure among stainless-steel welders and mild-steel welders, chromium levels in blood, plasma, and urine were higher among the stainless-steel welders, particularly

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those engaged in manual metal arc welding, which produces fumes with high concentrations of total water-soluble chromium, mainly chromium(VI) (which constituted up to 61% of total soluble chromium) (Edme *et al.* 1997).

The National Occupational Hazard Survey (conducted from 1972 to 1974) estimated that 16,576 workers potentially were exposed to chromium (types and compounds not specified), 42,043 to potassium dichromate, and 3,519 to calcium chromate (NIOSH 1976). The National Occupational Exposure Survey (conducted 1981 to 1983) estimated that 386,142 workers, including 10,433 women, potentially were exposed to chromium; 61,073, including 19,198 women, to potassium dichromate; 32,129, including 5,565 women, to calcium chromate; and 30,784, including 8,856 women, to lead chromate (NIOSH 1990).

Regulations

Department of Transportation (DOT)

Chromium hexavalent compounds are considered hazardous materials, and special requirements have been set for marking, labeling, and transporting these materials.

Environmental Protection Agency (EPA)

Clean Air Act

Mobile Source Air Toxics: Chromium compounds are listed as mobile source air toxics for which regulations are to be developed.

National Emission Standards for Hazardous Air Pollutants: Chromium compounds are listed as hazardous air pollutants.

Urban Air Toxics Strategy: Chromium compounds have been identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Clean Water Act

Numerous hexavalent chromium compounds are designated as hazardous substances.

Effluent Guidelines: Chromium and chromium compounds are listed as toxic pollutants.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 5,000 lb for chromium; = 10 lb for chromic acid, sodium chromate, ammonium chromate, potassium chromate, strontium chromate, calcium chromate, lithium chromate, potassium bichromate, ammonium bichromate, sodium bichromate; = 1,000 lb for chromic acetate, chromic sulfate.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Chromium compounds are listed substances subject to reporting requirements.

Federal Insecticide, Fungicide, and Rodenticide Act

Wood intended to be used in residential settings cannot be treated with chromated copper arsenate.

Resource Conservation and Recovery Act

Characteristic Hazardous Waste: Toxicity characteristic leaching procedure (TCLP) threshold = 5.0 mg/L for chromium.

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of chromium hexavalent compounds = F006, F019, K002, K003, K004, K005, K006, K007, K008, K048, K049, K050, K051, K061, K062, K069, K086, K100; on the presence of chromium = F032, F034, F035, F037, F038.

Chromium compounds are listed as hazardous constituents of waste.

Safe Drinking Water Act

Maximum contaminant level (MCL) = 0.1 mg/L for total chromium.

Food and Drug Administration (FDA)

Maximum permissible level of chromium in bottled water = 0.1 mg/L.

Specified color additives may contain chromium (as chromates) under certain restrictions.

Specified color additives may contain chromium at levels no greater than 50 ppm.

Hydrolyzed leather meal used in the feed of animals may contain chromium at levels not to exceed 2.75% of the total by weight; finished feeds may not contain more than 1% hydrolyzed leather meal by weight.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.

Permissible exposure limit (PEL) = 0.005 mg/m³ for hexavalent chromium and compounds;

= 0.1 mg/m³ where the limit of 0.005 mg/m³ has been stayed or otherwise is not in effect.

Comprehensive standards have been developed for occupational exposure to hexavalent chromium in any form and in any compound.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.05 mg/m³ for water-soluble

chromium(VI) compounds; = 0.01 mg/m³ for insoluble chromium(VI) compounds.

Biological exposure index (BEI) (end of shift at end of workweek) = 25 µg/L for total chromium in urine; (increase during shift) = 10 µg/L for total chromium in urine.

National Institute for Occupational Safety and Health (NIOSH)

Immediately dangerous to life and health (IDLH) limit = 15 mg/m³ as hexavalent chromium for chromic acid and chromates.

Recommended exposure limit (REL) (time-weighted-average workday) (8-h TWA) = 0.0002 mg/m³ (as hexavalent chromium).

NIOSH considers all hexavalent chromium compounds to be potential occupational carcinogens (based on listings for chromic acid and chromates and for chromyl chloride).

References

- ATSDR. 2000. *Toxicological Profile for Chromium (Final Report)*. Atlanta, GA: Agency for Toxic Substances and Disease Registry. 455 pp.
- Brooks WE. 2009. *2008 Minerals Yearbook: Arsenic*. U.S. Geological Survey. <http://minerals.usgs.gov/minerals/pubs/commodity/arsenic/myb1-2008-arsen.pdf>.
- Costa M. 1997. Toxicity and carcinogenicity of Cr(VI) in animal models and humans. *Crit Rev Toxicol* 27(5): 431-442.
- Edme JL, Shirali P, Mereau M, Sobaszek A, Boulenguez C, Diebold F, Haguenoer JM. 1997. Assessment of biological chromium among stainless steel and mild steel welders in relation to welding processes. *Int Arch Occup Environ Health* 70(4): 237-242.
- HSDB. 2009. *Hazardous Substances Data Bank*. National Library of Medicine. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB> and search on CAS numbers. Last accessed: 12/17/09.
- IARC. 1973. Chromium and chromium compounds. In *Some Inorganic and Organometallic Compounds*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 2. Lyon, France: International Agency for Research on Cancer. pp. 100-125.
- IARC. 1979. Chromium and certain chromium compounds. In *Chemicals and Industrial Processes Associated with Cancer in Humans*. suppl. 1. Lyon France: International Agency for Research on Cancer. pp. 29-30.
- IARC. 1980. Chromium and chromium compounds. In *Some Metals and Metallic Compounds*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 23. Lyon, France: International Agency for Research on Cancer. pp. 205-323.
- IARC. 1990. Chromium and chromium compounds. In *Chromium, Nickel and Welding*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 49. Lyon, France: International Agency for Research on Cancer. pp. 49-256.
- NIOSH. 1976. *National Occupational Hazard Survey (1972-74)*. DHEW (NIOSH) Publication No. 78-114. Cincinnati, OH: National Institute for Occupational Safety and Health.
- NIOSH. 1990. *National Occupational Exposure Survey (1981-83)*. National Institute for Occupational Safety and Health. Last updated: 7/1/90. <http://www.cdc.gov/noes/noes1/19395sic.html>, <http://www.cdc.gov/noes/noes1/80064sic.html>, <http://www.cdc.gov/noes/noes1/83496sic.html>, <http://www.cdc.gov/noes/noes1/x5638sic.html>.
- NTP. 2008. *NTP Technical Report on the Toxicology and Carcinogenesis Studies of Sodium Dichromate Dihydrate (CAS No. 7789-12-0) in F344/N Rats and B6C3F1 Mice (Drinking Water Studies)*. NTP Technical Report Series 546. NIH Publication No. 08-5887. Research Triangle Park, NC: National Toxicology Program. 201 pp.
- Papp JF. 2009. Chromium. In *2007 Minerals Yearbook*. U.S. Geological Survey. <http://minerals.usgs.gov/minerals/pubs/commodity/chromium/myb1-2007-chrom.pdf>.
- Papp JF. 2010. Chromium. In *Mineral Commodity Summaries*. U.S. Geological Survey. <http://minerals.usgs.gov/minerals/pubs/commodity/chromium/mcs-2010-chrom.pdf>.
- TRI. 2008. *TRI Explorer Chemical Report*. U.S. Environmental Protection Agency. Last updated: 9/22/08. <http://www.epa.gov/triexplorer> and select Chromium Compounds (Except Chromite Ore Mined in The Transvaal Region).
- USGS. 2010. Chromium. In *Historical Statistics for Mineral and Material Commodities in the United States*. U.S. Geological Survey. Last updated: 1/7/10. <http://minerals.usgs.gov/ds/2005/140/chromium.pdf>.
- USITC. 2009. *USITC Interactive Tariff and Trade DataWeb*. United States International Trade Commission. http://dataweb.usitc.gov/scripts/user_set.asp and search on HTS nos. 281910, 284120, 284130, 284150. Last accessed: 12/17/09.

Cobalt-Related Exposures

The Report on Carcinogens includes two separate listings (i.e., profiles) for cobalt-related exposures: Cobalt and Cobalt Compounds That Release Cobalt Ions *In Vivo* and Cobalt-Tungsten Carbide: Powders and Hard Metals. Cobalt and cobalt compounds as a class are listed for the first time in the *Fourteenth Report on Carcinogens*, and this listing includes and supersedes the listing for cobalt sulfate, which first appeared in the *Eleventh Report on Carcinogens*. Cobalt-tungsten carbide was first listed in the *Twelfth Report on Carcinogens*. The profiles for these listings follow this introduction.

Cobalt and Cobalt Compounds That Release Cobalt Ions *In Vivo*

CAS No. 7440-48-4 (Cobalt metal)

No separate CAS No. assigned for cobalt compounds as a class
Reasonably anticipated to be human carcinogens

Introduction

This listing of the class of cobalt and cobalt compounds that release cobalt ions *in vivo* (as defined below) supersedes the previous listing of cobalt sulfate in the Report on Carcinogens. The compound cobalt sulfate was first listed in the *Eleventh Report on Carcinogens* in 2004 as *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity in experimental animals.

Carcinogenicity

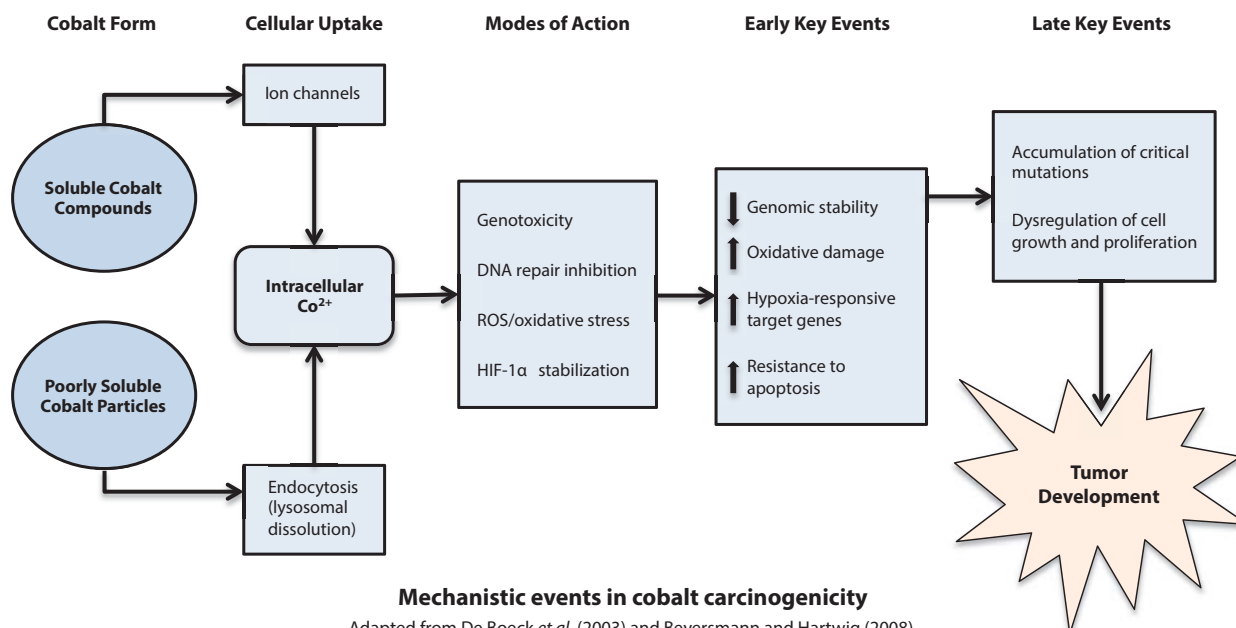
Cobalt and cobalt compounds that release cobalt ions *in vivo* are *reasonably anticipated to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in experimental animals and supporting data from studies on mechanisms of carcinogenesis. Mechanistic data indicate that the release of cobalt ions *in vivo* is a key event for cobalt-induced carcinogenicity. The available data show that cobalt metal and cobalt compounds that release cobalt ions *in vivo* (regardless of their solubility in water) act via similar modes of action to cause similar types of effects, including cell death, DNA damage, and cancer, and that the cobalt ion is largely responsible for the toxicity and carcinogenicity (NTP 1998, 2014, IARC 2006).

Both water-soluble cobalt compounds and poorly water-soluble cobalt particles are included in this class, as both types of cobalt species can release cobalt ions *in vivo*, although they differ in the mechanisms by which the cobalt ions enter cells. Vitamin B₁₂, which is an essential cobalt-containing nutrient, does not meet the criteria for this listing, because the vitamin does not release cobalt ions, but passes through the body intact while bound to specific carrier proteins (Neale 1990). It is not possible to determine the quantitative carcinogenic risk from cobalt ions released from surgical implants because of limitations in the available cancer studies of cobalt alloy implants in experimental animals and of patients with cobalt-containing surgical implants.

Mechanisms of Carcinogenesis and Other Relevant Data

The key events related to toxicity and carcinogenicity are thought to include cellular uptake of cobalt, intracellular release of cobalt ions from particles, and immediate and downstream biological responses related to the proposed modes of action. The first step in the carcinogenicity or toxicity process is the release of cobalt ions *in vivo*. Water-soluble cobalt compounds release cobalt ions into fluids outside the cell, and the ions enter the cell through ion channels within the cell membrane. In contrast, poorly soluble particulate cobalt compounds are taken up by specific organelles (lysosomes) in the cell via a process called endocytosis; cobalt is then solubilized in the acidic environment in the lysosomes, and the ions are released inside the cell. Evidence for cellular uptake of the different forms of cobalt is provided by studies evaluating their solubility in biological fluids *in vitro* (e.g., in gastric and lysosomal fluids) (see Properties) and *in vitro* studies measuring levels of cobalt ions within cells (Peters *et al.* 2007, Ortega *et al.* 2014, Sabbioni *et al.* 1994, Smith *et al.* 2014).

Although the mechanism(s) of action for cobalt-induced carcinogenic effects are not completely understood, several key events have been identified that are related to biologically plausible modes of action and are applicable to all cobalt forms that release cobalt ions *in vivo*. These events include inhibition of DNA repair, genotoxicity, generation of reactive oxygen species (ROS) resulting in oxidative damage, and stabilization of hypoxia-inducible factor 1 α (HIF-1 α), a protein that increases the expression of genes that promote survival of cells when they receive less oxygen. The proposed modes of action are summarized in the diagram below.



Adapted from De Boeck *et al.* (2003) and Beyersmann and Hartwig (2008).

Cobalt is considered to be a clastogen, because in *in vitro* assays in mammalian cells, it primarily causes chromosome damage and DNA strand breaks. Only a few genotoxicity studies in experimental animals were available, but the results were generally consistent with those of *in vitro* studies. Two potential mechanisms for genotoxicity include (1) direct induction of oxidative damage to DNA by cobalt(II) ions and (2) an indirect effect through inhibition of DNA repair (Smith *et al.* 2014, Lison 2015).

Cobalt is one of a group of metals (transition metals, like iron and nickel) that promote oxidation and reduction (redox) reactions through transfer of electrons. *In vitro* studies have shown that cobalt particles and ions can induce ROS in mammalian cells, with cobalt metal and cobalt oxide particles having a greater effect than ions. It has been proposed that ROS can play a role in the tumor development process at several stages, including initiating the process by inducing mutations and promoting proliferation of these mutated cells by deregulating controls on cell growth, leading to tumors. Studies in rats have shown that cobalt causes oxidative stress and oxidative DNA damage in several tissues, including kidney, liver, and lung (Kasprzak *et al.* 1994), which supports this proposed pathway for cobalt-induced carcinogenicity. Also, a higher frequency of a specific mutation in the *K-ras* oncogene, a gene with the potential to cause cancer, was found in cobalt-induced lung tumors in mice and rats than in spontaneous lung tumors (NTP 1998, 2014, IARC 2006). This mutation involves substitution of one nucleotide for another in a G to T transversion, which is a mutation commonly associated with oxidative DNA damage. In addition, cobalt-induced oxidative stress (via the production of ROS) can activate genes and proteins (specifically, the transcription factors NF- κ B, AP1, p53, and Nrf2) that in turn regulate the expression of many genes that play a role in carcinogenicity, such as those involved in inflammation and control of the cell cycle (Valko *et al.* 2005, 2006, Beyersmann and Hartwig 2008, Shukla *et al.* 2012, Davidson *et al.* 2015, PubChem 2015).

Finally, a well-established biological effect of cobalt is to mimic oxygen deficiency in cells by stabilizing HIF-1 α (Maxwell and Salnikow 2004, Greim *et al.* 2009, Saini *et al.* 2010a,b, Galán-Cobo *et al.* 2013, Gao *et al.* 2013, Nyga *et al.* 2015). HIF-1 α plays a central role in regulating more than 100 hypoxia-responsive genes and is a major regulator of the adaptation of cancer cells to oxygen deficiency. HIF-1 α overexpression has been linked to cancer initiation and progression and is a common characteristic of many human cancers (Paul *et al.* 2004, Galanis *et al.* 2008, 2009, Cheng *et al.* 2013).

Although most of the toxicological effects of cobalt are attributed to the cobalt ion, direct toxic effects of cobalt particles also contribute, as evidenced by the greater toxicity of cobalt metal than of cobalt sulfate in National Toxicology Program (NTP) rodent bioassays (NTP 1998, 2014, Behl *et al.* 2015). Differences in the relative toxicity reported for cobalt particles and ions may be partially explained by differences in the mechanisms by which cobalt enters the cell and in the subsequent accumulation and distribution of cobalt within the cell, as well as a synergistic effect between the particles and metal on ROS production (Peters *et al.* 2007, Sabbioni *et al.* 2014, Smith *et al.* 2014).

Cancer Studies in Experimental Animals

Exposure of experimental animals to cobalt metal or cobalt compounds caused tumors in two rodent species, at several different tissue sites, and by several different routes of exposure. This conclusion is based on studies in rats and mice exposed to cobalt metal (five studies), water-soluble cobalt compounds (two studies with cobalt sulfate and one study with cobalt chloride), and poorly water-soluble cobalt compounds (four studies with cobalt oxide). Studies of cobalt alloys and radioactive cobalt in experimental animals were

not considered to be informative, because of potential confounding by other carcinogens.

Inhalation exposure of rats and mice to cobalt metal (NTP 2014) or cobalt sulfate (NTP 1998) or intratracheal instillation of cobalt oxide in rats (Steinhoff and Mohr 1991) caused lung tumors (alveolar/bronchiolar adenoma and carcinoma). In addition, inhalation exposure of rats to cobalt metal caused squamous-cell tumors of the lung (primarily cystic keratinizing epithelioma) in females and possibly in males.

In inhalation studies of cobalt metal in rats (NTP 2014), tumors were also induced at sites distant from the lung, including tumors of the pancreas (islet-cell adenoma or carcinoma combined) in males and of the hematopoietic system (mononuclear-cell leukemia) in females, indicating a systemic effect. Increased incidences of kidney tumors (adenoma or carcinoma combined) in male rats and pancreas (carcinoma) in female rats may have been related to cobalt metal inhalation; however, the findings were not conclusive. Inhalation exposure to cobalt metal (NTP 2014) or cobalt sulfate (NTP 1998) induced adrenal-gland tumors (benign and malignant pheochromocytoma), which could have been caused by direct or indirect mechanisms.

In rats, local injection of cobalt at various anatomic locations caused tumors at the injection sites. Although these studies were less robust than the inhalation studies, and sarcomas are common in rats following injection of a variety of compounds, the consistency of the tumor types and findings across different cobalt forms provides supporting evidence for the carcinogenicity of cobalt. Intraperitoneal or intramuscular injection of the poorly water-soluble compound cobalt oxide caused histiocytoma or sarcoma at the injection site (Gilman and Ruckerbauer 1962, Steinhoff and Mohr 1991), and subcutaneous injection of the water-soluble compound cobalt chloride caused fibrosarcoma (Shabaan *et al.* 1977). Intramuscular or intrathoracic injection of cobalt metal (Heath 1956, Heath and Daniel 1962) or nanoparticles (Hansen *et al.* 2006) caused various types of sarcoma (primarily rhabdomyofibrosarcoma, rhabdomyosarcoma, or fibrosarcoma). In the study of nanoparticles, no tumors were observed after implantation of substances (e.g., titanium dioxide and silicon dioxide) with the same physical characteristics (i.e., surface-to-volume ratio) as cobalt, suggesting that the tumors were due to carcinogenic properties of cobalt and not just to a reaction to any physical implant.

A few studies in rodents (Gilman and Ruckerbauer 1962, Jasmin and Riopelle 1976, Wehner *et al.* 1977) found no tumors at certain tissue sites following exposure to the same forms of cobalt that caused tumors in other studies; however, these studies generally lacked sensitivity to detect an effect, because of the use of a less sensitive animal model, shorter study duration, or lower exposure levels.

Cancer Studies in Humans

The data available from studies in humans are inadequate to evaluate the relationship between human cancer and exposure specifically to cobalt and cobalt compounds that release cobalt ions *in vivo*. The data relevant to the evaluation were from studies primarily evaluating lung cancer in five independent cohorts of workers in different types of industries and two population-based case-control studies of esophageal cancer and other cancers of the respiratory and upper digestive (aerodigestive) tract, one in Ireland (O'Rorke *et al.* 2012) and the other in the state of Washington (Rogers *et al.* 1993). Studies of cobalt alloys in humans (primarily joint implants) were not considered to be informative, because they were not specific to cobalt exposure, and the extent of any cobalt exposure was unknown.

Although increased risks of lung cancer were found in most of the cohort studies, it is unclear that the excess risks were due to exposure specifically to cobalt, because of potential confounding from

exposures to known lung carcinogens or other study limitations. In the cohort studies, hard-metal (Moulin *et al.* 1998, Wild *et al.* 2000) and nickel-refinery workers (Grimsrud *et al.* 2005) were also exposed to known lung carcinogens. The findings of an increased risk of lung cancer among porcelain painters exposed to cobalt was complicated by a somewhat similar increase in risk among female pottery workers who were not thought to be exposed to cobalt (Tüchsen *et al.* 1996). In studies of a cohort of cobalt production workers, the excess risk found in the first report of this cohort (Mur *et al.* 1987) was no longer present in an update of the cohort (Moulin *et al.* 1993). No association between cobalt exposure and lung cancer was found in a study of stainless- and alloyed-steel workers in France (Moulin *et al.* 2000). Most of the studies had limited sensitivity to detect a true risk, because of small numbers of lung-cancer cases among exposed workers, crude methods of exposure assessment, or potential healthy-worker-related effects (due to the fact that workers are healthier on average than the general population).

Increased risks of esophageal cancer were suggested in two case-control studies; however, it is unclear whether cobalt exposure contributed to the cancer excess. In both studies, cobalt exposure was assessed from a single sample of toenail clippings taken at or several months after diagnosis of esophageal cancer. Measurements of cobalt in toenails reflect an integrated exposure that occurred 12 to 18 months before clipping, raising the question of whether levels found in toenails close to or, in many cases, after cancer diagnosis reflected the relevant period of exposure for long-latency cancer.

Properties

As a class, cobalt and cobalt compounds that release cobalt ions *in vivo* are related largely by their chemical properties, specifically bio-

availability. (The different valence states of cobalt are described below, under Chemical Characteristics.)

Bioavailability

The carcinogenic and toxic effects of cobalt and cobalt compounds begin with the release of cobalt ions *in vivo*. The bioavailability of a metal species can be predicted by its solubility in biological fluids, such as synthetic equivalents of gastric and intestinal fluids (for ingestion exposure) or lung (alveolar, interstitial, and lysosomal) fluids (for inhalation exposure), and by studies in cultured cells. Results from studies testing solubility in synthetic biological fluids are shown in the table below, along with other chemical and physical properties of cobalt metal and these cobalt compounds. These studies demonstrated that cobalt metal and both water-soluble and poorly water-soluble cobalt compounds can dissolve and release cobalt ions in some biological fluids (Brock and Stopford 2003, Stopford *et al.* 2003, Cobalt Development Institute personal communication 21 Jul and 19 Oct 2015), suggesting that they will release ions *in vivo*.

Very low values ($\leq 2\%$) for bioaccessibility have been reported for the sulfide and mixed (II,III) oxide (Co_3O_4), and intermediate values (14% to 55%) for stearate and oxalate under the same test conditions. However, other, more informative tests with more physiologically relevant test conditions (e.g., two-week studies with 0.3- μm particles in culture medium in the presence of alveolar macrophages) have reported 50% solubility for Co_3O_4 . In addition, Ortega *et al.* (2014) found that intracellular concentrations of solubilized cobalt ions were similar for Co_3O_4 and cobalt chloride in human lung cells *in vitro*, suggesting that Co_3O_4 would release cobalt ions *in vivo*. Results with other biological fluids, such as serum and intestinal, alveolar, and interstitial fluids, indicate that the species of cobalt compound, parti-

Physical and chemical properties of cobalt metal and some cobalt compounds

Form ^a	CAS No.	Formula	Molec. weight	Physical form	Density or specific gravity	Water solubility (g/100 cc) ^b	Bioaccessibility (% solubility in gastric/lysosomal fluids)
Cobalt metal	7440-48-4	Co ^c	58.9 ^c	grey hexagonal or cubic metal ^c	8.92 ^c	0.00029 ^d	100/100 ^e
Water-soluble compounds							
Acetate (org.)	71-48-7	$\text{Co}(\text{C}_2\text{H}_3\text{O}_2)_2^f$	249.1 ^f	red-violet, monoclinic ^f	1.70 ^f	34.8 ^d	98/80 ^d
Chloride	7646-79-9	CoCl_2^g	129.8 ^g	blue hexagonal leaflets ^g	3.36 ^g	45 ^g	100/100 ^e
Nitrate	10141-05-6	CoN_2O_6^c	182.9 ^c	red powder or crystals ^c	2.49 ^c	67.0 ^d	96/100 ^d
Sulfate heptahydrate	10026-24-1	$\text{CoSO}_4 \cdot 7\text{H}_2\text{O}^f$	281.1 ^f	red pink, monoclinic ^f	1.95 ^f	60.4 ^f	100/100 ^e
Poorly water-soluble compounds							
Carbonate (org.)	513-79-1	CoCO_3^f	118.9 ^f	red, trigonal ^f	4.13 ^f	0.00114 ^d	100/100 ^e
2-Ethylhexanoate (org.)	136-52-7	$\text{Co}(\text{C}_8\text{H}_{15}\text{O}_2)_2^f$	173.7 ^h	blue liquid (12% Co) ^f	1.01 ^f	0.630 ^d	100/100 ^e
Hydroxide	21041-93-0	$\text{Co}(\text{OH})_2^f$	93.0 ^f	rose-red, rhombic ^f	3.60 ^f	0.00032 ^f	95/98 ^d
Naphthenate (org.)	61789-51-3	$\text{Co}(\text{C}_{11}\text{H}_{17}\text{O}_2)_2^c$	401.3 ^c	purple liquid (6% Co) ^f	0.97 ^f	0.0293 ^d	100/100 ^e
Oxalate (org.)	814-89-1	CoC_2O_4^f	147.0 ^f	white or reddish ^f	3.02 ^f	0.00322 ^d	37/55 ^d
Oxide	1307-96-6	CoO^f	74.9 ^f	green-brown cubic ^f	6.45 ^f	0.00049 ^d	100/92.4 ^e
(II,III) Oxide	1308-06-1	Co_3O_4^f	240.8 ^f	black, cubic ^f	6.07 ^f	0.00016 ^d	2/2 ^d (50%) ⁱ
Propionate (org.)	1560-69-6	$\text{Co}(\text{C}_3\text{H}_5\text{O}_2)_2^c$	205.1 ^c	reddish solid ^d	—	7.49 ^d	91/94 ^d
Stearate (org.)	1002-88-6	$\text{Co}(\text{C}_{18}\text{H}_{35}\text{O}_2)_2^c$	625.9 ^c	grey solid ^d	—	0.00705 ^d	14/16 ^d
Sulfide	1317-42-6	CoS^f	91.0 ^f	reddish octahedral ^f	5.45 ^f	0.00038 ^f	1/1 ^d

^aCobalt compounds selected for inclusion in the table are those with toxicological data or of commercial importance. All compounds contain Co(II) except where noted. Forms in italics have been tested for carcinogenicity or genetic toxicity or have mechanistic data; org. = organic compound; all others are inorganic.

^bSolubility data were converted to grams per 100 cubic centimeters as necessary.

^cPubChem 2015, ^dCobalt Development Institute personal communication 21 Jul and 19 Oct 2015, ^eStopford *et al.* 2003, ^fCDI 2006, ^gHSDB 2012, ^hHSDB 2004.

ⁱKreyling *et al.* 1990. Bioaccessibility was assessed by release of cobalt ions into culture medium in the presence of canine alveolar macrophages after two weeks of culture.

cle size and surface area, and pH of the surrogate fluid all can affect the solubility of cobalt in biological fluids.

The solubility of cobalt compounds in water depends largely on pH, and cobalt is generally more mobile in acidic solutions than in alkaline solutions (IARC 1991, Paustenbach *et al.* 2013). Sulfates, nitrates, and chlorides of cobalt tend to be soluble in water, whereas oxides (including the mixed oxide, Co_3O_4), hydroxides, and sulfides tend to be poorly soluble or insoluble in water (Lison 2015). Organic cobalt compounds can be either soluble, as is cobalt(II) acetate, or insoluble, as are cobalt(II) carbonate and cobalt(II) oxalate (CDI 2006). In addition to low pH, solubilization of some poorly water-soluble compounds in biological fluids may be enhanced in the presence of binding proteins (IARC 2006).

Chemical Characteristics

Cobalt (Co) is a naturally occurring transition element with magnetic properties. It is the 33rd most abundant element, making up approximately 0.0025% of the weight of Earth's crust. Cobalt is a component of more than 70 naturally occurring minerals, including arsenides, sulfides, and oxides. The only stable and naturally occurring cobalt isotope is ^{59}Co (ATSDR 2004, WHO 2006). Metallic cobalt, Co(0), exists in two crystalline forms, hexagonal and cubic, which are stable at room temperature (IARC 1991, ATSDR 2004, WHO 2006). Cobalt predominantly occurs in two oxidation states, Co(II) and Co(III). Co(II) is much more stable than Co(III) in aqueous solution (Nilsson *et al.* 1985, Paustenbach *et al.* 2013) and is present in the environment and in most commercially available cobalt compounds (e.g., cobalt chloride, sulfide, and sulfate). Co(III) also is present in some commercially available cobalt compounds, including the mixed oxide (Co_3O_4) (IARC 1991, Paustenbach *et al.* 2013, Lison 2015) and some simple salts of Co(III) (e.g., Co_2O_3). Important salts of carboxylic acids include formate, acetate, citrate, naphthenate, linoleate, oleate, oxalate, resinate, stearate, succinate, sulfamate, and 2-ethylhexanoate.

Use

Cobalt and cobalt compounds are used in numerous commercial, industrial, and military applications. On a global basis, the largest use of cobalt is in rechargeable battery electrodes (Shedd 2014b); however, U.S. production of rechargeable batteries has been very limited (Brodd 2005). In 2012, the reported U.S. consumption of cobalt and cobalt compounds was approximately 8,420 metric tons, the majority used for superalloys (Shedd 2014b). Major uses for metallic cobalt include production of superalloys, cemented carbides, and bonded diamonds. Cobalt nanoparticles are used in medical applications (e.g., sensors, magnetic resonance imaging contrast enhancement, and drug delivery), and cobalt nanofibers and nanowires are used in industrial applications. Cobalt compounds are used as pigments for glass, ceramics, and enamels (oxides, sulfate, and nitrate), as driers for paints, varnishes, or lacquers (hydroxide, oxides, propionate, acetate, tallate, naphthenate, and 2-ethylhexanoate), as catalysts (hydroxide, oxides, carbonate, nitrate, acetate, oxalate, and sulfide), as adhesives and enamel frits (naphthenate, stearate, and oxides), and as trace mineral additives in animal diets (carbonate, sulfate, nitrate, oxides, and acetate). U.S. consumption of cobalt and cobalt compounds in 2012 is summarized in the following table.

The fastest-growing use for cobalt in recent years has been in high-capacity, rechargeable batteries, including nickel-cadmium, nickel-metal hydride, and lithium-ion batteries for electric vehicles and portable electronic devices such as smartphones and laptops (Maverick 2015). Many other uses for cobalt exist, including in integrated circuit contacts and semiconductor production. An emerging use is as a key element in several forms of "green" energy technology

End use	Metric tons of cobalt content	Percent of total consumption
Superalloys	4,040	48.0
Chemicals and ceramics	2,300	27.3
Cemented carbides	774	9.2
Other alloys ^a	699	8.3
Steels	548	6.5
Miscellaneous and unspecified	63	0.7

Source: Shedd 2014b.

^aIncludes magnetic, nonferrous, and wear-resistant alloys and welding materials.

applications, including gas-to-liquids and coal-to-liquids processes, oil desulfurization, clean coal, solar panels, wind and gas turbines, and fuel cells, and in cobalt-based catalysts for sunlight-driven water-splitting to convert solar energy into electrical and chemical energy.

Production

Cobalt metal is produced as a by-product from ores associated with copper, nickel, zinc, lead, and platinum-group metals and is most often chemically combined in its ores with sulfur and arsenic (Davis 2000, CDI 2006). The largest cobalt reserves are in the Congo (Kinshasa), Australia, Cuba, Zambia, Canada, Russia, and New Caledonia, with very limited production in the United States in recent years (Shedd 2014a). Except for a negligible amount of by-product cobalt produced from mining and refining of platinum-group metal ores, the United States did not refine cobalt in 2012 (Shedd 2014b). Cobalt has not been mined in the United States in over 30 years (ATSDR 2004); however, a primary cobalt mine, mill, and refinery were being established in Idaho in 2015 (Farquharson 2015). In 2012, 2,160 metric tons of cobalt was recycled from scrap. No cobalt has been sold from the National Defense Stockpile since 2009.

Metallic cobalt and several cobalt compounds are high-production-volume chemicals, based on their annual production or importation into the United States in quantities of at least 1 million pounds. Recent volumes of U.S. production, imports, and exports of cobalt metal and high-production-volume cobalt compounds are listed in the following table.

Cobalt category	Quantity (lb)		
	Production (2012)	Imports (2013)	Exports (2013)
Metal (excluding alloys)	23,384,002	16,151,599	— ^a
Compounds			
Acetates	1 million to < 10 million	342,918	520,996
Carbonates	1,038,821	1,193,856	— ^a
Chlorides	— ^b	215,661	14,304
2-Ethylhexanoate	4,294,523	—	—
Hydroxide	4,709,137	—	—
Oxides	1 million to < 10 million	5,300,984 ^c	902,467 ^c
Propionate	1 million to < 10 million	—	—
Sulfate	1 million to < 10 million	1,319,004	— ^a

Sources: EPA 2014 (production), USITC 2014 (imports and exports).

— = no data found.

^aNo specific Schedule B code was identified. (Schedule B codes are 10-digit numbers used by the U.S. Commerce Department to collect and publish statistics on physical goods exported from the United States.)

^bCobalt chloride production data for 2012 were withheld by the manufacturer.

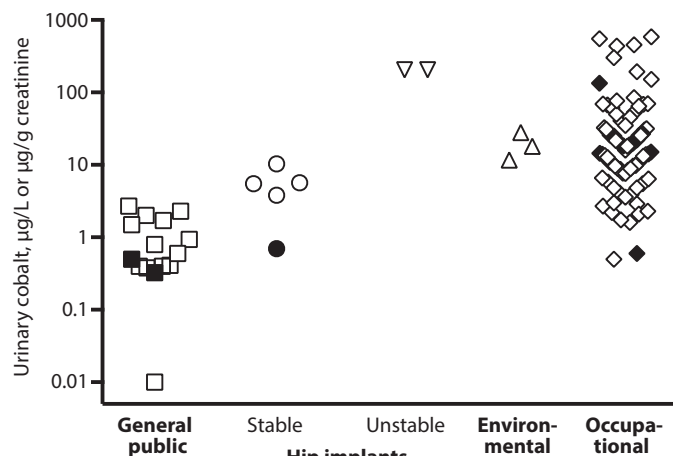
^cThe reported value is for cobalt hydroxide and oxides combined.

Exposure

A significant number of people living in the United States are exposed to cobalt, based on several lines of evidence, including biological monitoring data demonstrating exposure in occupationally and non-occupationally exposed populations. Data from the U.S. Environmental Protection Agency's Toxics Release Inventory (TRI) indi-

cate that production- and use-related releases of cobalt compounds have occurred at numerous industrial facilities in the United States.

In biomonitoring studies that measured cobalt in the urine of people exposed to cobalt from various sources, the highest levels generally were due to occupational exposures and failed hip implants; lower levels were due to exposure from normal implants or the environment. The lowest levels were observed in the general population (with unknown sources of exposure). The graph below shows the mean or median levels of urinary cobalt for the general population and for groups with known exposures. Data are reported for both U.S. and non-U.S. exposures; occupational and medical implant exposures outside the United States can be informative because of the similarity of production methods and implant compositions worldwide.



Urine levels of cobalt for various exposed groups

Source: NTP 2015.

Filled symbols = U.S. data; open symbols = non-U.S. data.
Each data point represents a different study.

Urinary cobalt measurements in the U.S. general population have remained consistent since 1999, with geometric mean values between 0.316 and 0.379 µg/L, according to the National Health and Nutrition Examination Survey (NHANES) (CDC 2014). Urinary cobalt is considered a good indicator of absorbed cobalt (IARC 2006, WHO 2006), especially from recent exposures (ATSDR 2004). Levels of cobalt in blood (including whole blood, plasma, and serum) show a pattern similar to that for urinary cobalt levels.

Occupational Exposure

The primary route of occupational exposure to cobalt is via inhalation of dust, fumes, mists, or gaseous cobalt carbonyl. Dermal contact with cemented carbide (i.e., hard-metal) powders and cobalt salts can result in systemic uptake. Occupational exposure to cobalt occurs in the following industries: (1) production of cobalt metal or salts, (2) metallurgical-related industries, (3) cemented carbides and bonded diamonds, (4) chemicals and pigments, and (5) electronics, “green” energy, and recycling. Occupational exposure has been documented by measurements of cobalt in ambient workplace air (as shown in the following table) and in blood, urine (as shown in the figure above), nails, and hair, and lung tissue from workers or deceased workers (IARC 1991, ATSDR 2004, IARC 2006, CDC 2013). The highest levels of cobalt in workplace air were generally for hard-metal manufacturing involving cobalt metal powders (> 1,000 µg/m³ in some instances) (NTP 2009), production of cobalt salts, and metallurgical-related industries (> 10,000 µg/m³ in some instances) (IARC 2006). The highest cobalt levels in urine, blood, hair, and nails also were associated with exposure to cobalt powders.

Industry	Cobalt in workplace air (range, µg/m ³)
Production of cobalt metal or salts	2–50,000
Metallurgical-related industries ^a	ND–21,000 ^b
Cemented carbides and bonded diamonds ^a	ND–1,622
Chemicals and pigments ^a	ND–80
Electronics, “green” energy, and recycling ^a	ND–10

Sources: IARC 2006, NIOSH 2015. ND = not detected.

^aThe range for cobalt in workplace air includes U.S. data from NIOSH Hazard Evaluation and Technical Assistance surveys.

^bOne higher value was reported; however, the Occupational Safety and Health Administration noted that the sample appeared to have been tampered with.

Surgical Implants

Total hip implants consist of (1) a femoral head attached to a stem that is inserted in the thigh bone (usually made of ceramic or metal) and (2) a socket or cup that is anchored in the pelvis (made of metal, ceramic, or polyethylene). Cobalt-chromium-molybdenum (CoCrMo) alloy is the predominant alloy used in metal-containing implants, such as metal-on-metal implants (in which both articulating surfaces are metal), polyethylene-on-metal implants, and metal-on-ceramic implants. Other metals, such as nickel, tungsten, iron, aluminum, and titanium, may also be used in implants. Knee implants may also contain cobalt metal; however, unlike some hip implants with metal-to-metal contact, knee implants are designed so that metal surfaces do not contact each other. Cobalt ions may be released into the body throughout the lifetime of a cobalt-containing device (Sampson and Hart 2012, Devlin *et al.* 2013). Urinary levels of cobalt identified from studies of hip implants reported as stable or that did not specifically address stability ranged from approximately 0.7 to 12 µg/L, compared with a range of 0.01 to 4.2 µg/L for the general population (as shown in the previous graph). Implants may fail because of excessive wear or corrosion by body fluids, increasing the levels of cobalt released from the implants (Sampson and Hart 2012). Dunstan *et al.* (2005) reported blood cobalt levels of 19 and 52 µg/L in two individuals with unstable (radiologically loose) metal-on-metal implants. In rare cases, high levels of cobalt from failed implants may be associated with toxicity. Recommended levels of blood cobalt for further clinical investigation and action were set at 7 µg/L in the United Kingdom (MHRA 2012) and 10 µg/L in the United States by the Mayo Clinic (2015).

Environmental Exposure

The TRI reported that in 2013, on- and off-site industrial releases of cobalt and cobalt compounds totaled approximately 5.5 million pounds from 723 facilities in the United States (TRI 2014a). Calculations based on media-specific release data from the TRI indicate that releases to land accounted for 82% of total releases in 2013 (TRI 2014b,c). Worldwide, approximately 75,000 metric tons of cobalt enters the environment annually, with similar amounts coming from natural sources (40,000 metric tons) and sources related to human activities (35,000 metric tons) (Shedd 1993, CDI 2006). Recycling of electronic and electrical waste can result in release of cobalt to the environment; however, releases from this source are less of a concern in the United States than in other global regions where recycling is more common and less controlled (Julander *et al.* 2014).

The average concentration of cobalt in ambient air in the United States has been reported to be approximately 0.4 ng/m³ (ATSDR 2004). Levels can be orders of magnitude higher near source areas (e.g., near facilities processing cobalt-containing alloys and compounds) reported from outside the United States. The median cobalt concentration in U.S. drinking water has been reported to be less than 2.0 µg/L; however, levels as high as 107 µg/L have been reported

(ATSDR 2004). Cobalt concentrations have been reported to range from 0.01 to 4 µg/L in seawater and from 0.1 to 10 µg/L in fresh water and groundwater (IARC 2006). Studies have reported cobalt soil concentrations ranging from 0.1 to 50 ppm. However, soils near ore deposits, phosphate rock, or ore-smelting facilities or soils contaminated by airport or highway traffic or near other source areas may contain higher concentrations (IARC 2006).

Data for individuals exposed to cobalt from the environment are limited, but a study of metal exposure from mining and processing of nonferrous metals in Katanga, Democratic Republic of Congo, found that geometric mean urinary cobalt concentrations were 4.5-fold higher for adults and 6.6-fold higher for children in urban and rural communities near mines and metal smelters than in rural communities without mining or industrial activities (Cheyns *et al.* 2014).

Other Sources of Exposure of the General Population

The general population can be exposed to low levels of cobalt primarily through consumption of food and to a lesser degree through inhalation of ambient air and ingestion of drinking water (ATSDR 2004). The daily cobalt intake from food in the United States was estimated to range from 3.4 to 11.6 µg based on analyses of 234 foods in the 1984 U.S. Food and Drug Administration Total Diet Study (Pennington and Jones 1987). Although this amount includes cobalt as part of both vitamin B₁₂ and other cobalt compounds (ATSDR 2004), green, leafy vegetables and fresh cereals generally contain the most cobalt (IARC 1991), and these plant sources of cobalt do not contain vitamin B₁₂. In the 1960s, some breweries added cobalt salts to beer to stabilize the foam (resulting in cobalt exposures of 0.04 to 0.14 mg/kg of body weight), but cobalt is no longer added to beer (ATSDR 2004). Higher cobalt intake may result from consumption of over-the-counter or prescription mineral preparations containing cobalt compounds.

Other potential sources of exposure include consumer products and tobacco smoking. Cobalt is present in only a few consumer products, including cleaners, detergents, soaps, car waxes, and a nickel metal hydride battery (5% to 10% cobalt) (ATSDR 2004, HPD 2014). Various brands of tobacco have been reported to contain cobalt at concentrations ranging from less than 0.3 to 2.3 µg/g of dry weight, and 0.5% of the cobalt content is transferred to mainstream smoke (WHO 2006). However, urinary cobalt levels (unadjusted for creatinine) for cigarette-smoke-exposed and unexposed NHANES participants for survey years 1999 to 2004 did not differ significantly (Richter *et al.* 2009).

Regulations

Coast Guard, Department of Homeland Security

Minimum requirements have been established for safe transport of cobalt naphthenate in solvent naphtha on ships and barges.

Department of Transportation (DOT)

Numerous cobalt compounds are considered hazardous materials, and special requirements have been set for marking, labeling, and transporting these materials.

Environmental Protection Agency (EPA)

Clean Air Act

National Emission Standards for Hazardous Air Pollutants: Cobalt compounds are listed as hazardous air pollutants.

Clean Water Act

Cobalt discharge limits are imposed for numerous processes during the production of cobalt at secondary cobalt facilities processing tungsten carbide scrap raw materials.

Discharge limits for cobalt are imposed for numerous processes during the production of cobalt at primary cobalt facilities; for numerous processes during the production of batteries; and for numerous processes during the production of cobalt salts.

Discharge limits for cobalt are imposed for wastewater discharges from centralized waste treatment facilities except discharges and activities exempted in 40 CFR 437.1(b), (c), and 40 CFR 421, Subpart AC.

Cobaltous bromide, formate, and sulfamate are designated as hazardous substances.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1,000 lb for cobaltous bromide, formate, and sulfamate.

Emergency Planning and Community Right-To-Know Act

EPCRA Section 302: Threshold planning quantity (TPQ) = 100 lb for cobalt, ((2,2'-(1,2-ethanediylbis(nitrilomethylidene))bis(6-fluorophenolato))(2-*N,N',O,O'*)- (also called fluomine) (solids in powder form with particle size < 100 µm or solution or molten form); = 10,000 lb for all other forms of fluomine; = 10 lb for cobalt carbonyl (solids in powder form with particle size < 100 µm or solution or molten form); = 10,000 lb for all other forms of cobalt carbonyl.

EPCRA Section 304: Reportable quantity (RQ) = 100 lb for fluomine; = 10 lb for cobalt carbonyl.

Toxics Release Inventory: Cobalt and cobalt compounds are listed substances subject to reporting requirements.

Federal Insecticide, Fungicide, and Rodenticide Act

Boiled linseed oil (containing no more than 0.33% manganese naphthenate and no more than 0.33% cobalt naphthenate) is exempt from the requirement of a tolerance when used as a coating agent for *S*-ethyl hexahydro-1*H*-azepine-1-carbothioate. No more than 15% of the pesticide formulation may consist of boiled linseed oil, and this exemption is limited to use on rice before edible parts form.

Food and Drug Administration (FDA, an HHS agency)

Cobaltous salts are prohibited from use in human food.

All drugs containing cobalt salts (except radioactive forms of cobalt and its salts and cobalamin and its derivatives) have been withdrawn from the market because they were found to be unsafe or not effective, and they may not be compounded.

Chromium–cobalt–aluminum oxide used as a color additive for linear polyethylene surgical sutures used in general surgery must comprise no more than 2% by weight of the suture material, not migrate to surrounding tissue, and conform to labeling requirements in 21 CFR 70.25.

Chromium cobalt-aluminum oxide may be used as a color additive in contact lenses in amounts not to exceed the minimum reasonably required to accomplish the intended coloring effect.

Ferric ammonium ferrocyanide and ferric ferrocyanide used to color externally applied drugs (including those for use in the area of the eye) must not contain more than 200 ppm cobalt (as Co) and conform to labeling requirements in 21 CFR 70.25.

21 CFR 369 contains recommended drug labeling statements for over-the-counter cobalt preparations containing ≥ 0.5 mg cobalt as a cobalt salt per dosage unit and which recommend administration rates of ≥ 0.5 mg per dose and ≥ 2 mg per 24-hour period.

An approved new drug application is required for marketing cobalt preparations intended for use by man.

21 CFR 872, 874, and 888 identify class designations (Class I, II, or III) of various cobalt-containing dental prosthetic device alloys, cobalt-chromium-alloy-based facial prosthetics, and cobalt-chromium-molybdenum orthopedic devices that determine the type of premarketing submission or application required for FDA clearance to market.

Cobalt naphthenate may be used in quantities that do not exceed those reasonably required as an accelerator in the production of cross-linked polyester resins used as articles or components of articles intended for repeated use in contact with food.

Cobalt aluminate may be safely used as a colorant in the manufacture of articles or components of articles intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding of food at levels not to exceed 5% by weight of all polymers except in resinous and polymeric coatings complying with 21 CFR 175.300, melamine-formaldehyde resins in molded articles complying with 21 CFR 177.1460, xylene-formaldehyde resins complying with 21 CFR 175.380, ethylene-vinyl acetate copolymers complying with 21 CFR 177.1350, and urea-formaldehyde resins in molded articles complying with 21 CFR 177.1900.

Occupational Safety and Health Administration (OSHA)

This legally enforceable PEL was adopted from the 1968 ACGIH TLV-TWA shortly after OSHA was established; it may not reflect the most recent scientific evidence and may not adequately protect worker health.

Permissible exposure limit (PEL) (8-h TWA) = 0.1 mg/m³ for cobalt metal, dust, and fume (as Co).

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.02 mg/m³ for cobalt and inorganic compounds; = 0.1 mg/m³ for cobalt carbonyl and cobalt hydrocarbonyl.

Biological exposure index (BEI) = 15 µg/L for cobalt in urine for cobalt and inorganic compounds, including cobalt oxides but not combined with tungsten carbide, for end of shift at end of workweek.

Consumer Product Safety Commission (CPSC)

The CPSC has issued guidance regarding the potential hazards of specific cobalt- or cobalt-compound-containing art and craft materials (e.g., glazes, glass colorants, paints, toners, pigments, and dyes) and specific precautions to take when using them.

Environmental Protection Agency (EPA)

Regional Screening Levels (formerly Preliminary Remediation Goals): residential soil = 23 mg/kg; industrial soil = 350 mg/kg; residential air = 0.00031 µg/m³; industrial air = 0.0014 µg/m³; tap water = 6 µg/L.

National Institute for Occupational Safety and Health (NIOSH, an HHS agency)

Recommended exposure limit (REL) (10-h TWA) = 0.05 mg/m³ for cemented tungsten carbide containing > 2% Co (as Co); = 0.05 mg/m³ for cobalt metal dust and fume (as Co); = 0.1 mg/m³ for cobalt carbonyl (as Co) and cobalt hydroxycarbonyl (as Co).

Immediately dangerous to life and health (IDLH) limit = 20 mg/m³ for cobalt metal dust and fume (as Co).

References

- ATSDR. 2004. *Toxicological Profile for Cobalt*. Atlanta, GA: Agency for Toxic Substances and Disease Registry. pp. 207-E203. <http://www.atsdr.cdc.gov/ToxProfiles/TP.asp?id=373&tid=64>.
- Behl M, Stout MD, Herbert RA, Dill JA, Baker GL, Hayden BK, Roycroft JR, Bucher JR, Hooth MJ. 2015. Comparative toxicity and carcinogenicity of soluble and insoluble cobalt compounds. *Toxicology* 333: 195-205.
- Beyersmann D, Hartwig A. 2008. Carcinogenic metal compounds: Recent insight into molecular and cellular mechanisms. *Arch Toxicol* 82(8): 493-512.
- Brock T, Stopford W. 2003. Bioaccessibility of metals in human health risk assessment: evaluating risk from exposure to cobalt compounds. *J Environ Monit* 5(4): 71N-76N.
- Brodd RJ. 2005. *Factors Affecting U.S. Production Decisions: Why Are There No Volume Lithium-Ion Battery Manufacturers in the United States?* ATP Working Paper 05-01, prepared for the National Institute of Standards and Technology Advanced Technology Program. <http://www.atp.nist.gov/eao/wp05-01/wp05-01.pdf>. 92 pp.
- CDC. 2013. *Biomonitoring Summary: Cobalt*. Centers for Disease Control and Prevention. Last updated: 12/4/13. http://www.cdc.gov/biomonitoring/Cobalt_BiomonitoringSummary.html.
- CDC. 2014. *Fourth National Report on Human Exposure to Environmental Chemicals*. Atlanta, GA: Centers for Disease Control and Prevention. 514 pp.
- CDI. 2006. Cobalt in chemicals. In *Cobalt Facts*. Cobalt Development Institute. http://thecci.com/cdi/images/documents/facts/COBAL_FACTS-Chemicals%202015.pdf.
- Cheng Y, Chen G, Hong L, Zhou L, Hu M, Li B, Huang J, Xia L, Li C. 2013. How does hypoxia inducible factor-1 α participate in enhancing the glycolysis activity in cervical cancer? *Ann Diagn Pathol* 17(3): 305-311.
- Cheyns K, Banza Lubaba Nkulu C, Ngombe LK, Asosa JN, Haufroid V, De Putter T, et al. 2014. Pathways of human exposure to cobalt in Katanga, a mining area of the D.R. Congo. *Sci Total Environ* 490: 313-321.
- Davidson T, Ke Q, Costa M. 2015. Selected molecular mechanisms of metal toxicity and carcinogenicity. In *Handbook on the Toxicology of Metals*, 4th ed., vol. I. Nordberg GF, Fowler BA, Nordberg M, eds. Waltham, MA: Elsevier. pp. 173-196.
- Davis JR, ed. 2000. The cobalt industry: Occurrence, recovery, and consumption. In *Nickel, Cobalt, and Their Alloys*. Materials Park, OH: ASM International. pp. 345-348.
- De Boeck M, Kirsch-Volders M, Lison D. 2003b. Cobalt and antimony: Genotoxicity and carcinogenicity. *Mutat Res* 533(1-2): 135-152.
- Devlin JJ, Pomerleau AC, Brent J, Morgan BW, Deitchman S, Schwartz M. 2013. Clinical features, testing, and management of patients with suspected prosthetic hip-associated cobalt toxicity: A systematic review of cases. *J Med Toxicol* 9(4): 405-415.
- Dunstan E, Sanghrajka AP, Tilley S, Unwin P, Blunn G, Cannon SR, Briggs TW. 2005. Metal ion levels after metal-on-metal proximal femoral replacements: A 30-year follow-up. *J Bone Joint Surg Br* 87(5): 628-631.
- EPA. 2014. *Non-confidential 2012 Chemical Data Reporting (CDR) Database*. U.S. Environmental Protection Agency. Last updated: 6/14. http://java.epa.gov/oppt_chemical_search and select CDR tab and search on CAS number.
- Farquharson JP. 2015. *Formation Metals Inc. - President's Letter to Shareholders*. Formation Metals, Inc. <http://www.formationmetals.com/s/CobaltNews.asp?ReportID=697830>.
- Galán-Cobo A, Sánchez-Silva R, Serna A, Abreu-Rodríguez I, Muñoz-Cabello AM, Echevarría M. 2013. Cellular overexpression of Aquaporins slows down the natural HIF-2 α degradation during prolonged hypoxia. *Gene* 522(1): 18-26.
- Galanis A, Pappa A, Giannakakis A, Lanitis E, Dangaj D, Sandaltzopoulos R. 2008. Reactive oxygen species and HIF-1 signalling in cancer. *Cancer Lett* 266(1): 12-20.
- Galanis A, Karapetsas A, Sandaltzopoulos R. 2009. Metal-induced carcinogenesis, oxidative stress and hypoxia signalling. *Mutat Res* 674(1-2): 31-35.
- Gao S, Zhou J, Zhao Y, Toselli P, Li W. 2013. Hypoxia-response element (HRE)-directed transcriptional regulation of the rat lysyl oxidase gene in response to cobalt and cadmium. *Toxicol Sci* 132(2): 379-389.
- Gilman JP, Ruckerbauer GM. 1962. Metal carcinogenesis. I. Observations on the carcinogenicity of a refinery dust, cobalt oxide, and colloidal thorium dioxide. *Cancer Res* 22: 152-157.
- Greim H, Hartwig A, Reuter U, Richter-Reichhelm HB, Thielmann HW. 2009. Chemically induced pheochromocytomas in rats: Mechanisms and relevance for human risk assessment. *Crit Rev Toxicol* 39(8): 695-718.
- Grimsrud TK, Berge SR, Haldorsen T, Andersen A. 2005. Can lung cancer risk among nickel refinery workers be explained by occupational exposures other than nickel? *Epidemiology* 16(2): 146-154.
- Hansen T, Clermont G, Alves A, Eloy R, Brochhausen C, Boudrand JP, Gatti AM, Kirkpatrick CJ. 2006. Biological tolerance of different materials in bulk and nanoparticulate form in a rat model: Sarcoma development by nanoparticles. *J R Soc Interface* 3(11): 767-775.
- Heath JC. 1956. The production of malignant tumours by cobalt in the rat. *Br J Cancer* 10(4): 668-673.
- Heath JC, Daniel MR. 1962. The production of malignant tumours by cobalt in the rat: Intrathoracic tumours. *Br J Cancer* 16(3): 473-478.
- HPD. 2014. *Household Products Database*. National Library of Medicine. Last updated: 8/14. <http://householdproducts.nlm.nih.gov/advancedsearch.htm> and select Ingredient and search on CAS number.
- HSDB. 2004. *Hazardous Substances Database. Cobalt Bis(2-Ethylhexanoate)*. National Library of Medicine. Last updated: 3/5/04. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB> and search on CAS number.
- HSDB. 2012. *Hazardous Substances Database. Cobaltous Chloride*. National Library of Medicine. Last updated: 3/23/12. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB> and search on CAS number.
- IARC. 1991. Cobalt and cobalt compounds. In *Chlorinated Drinking-water; Chlorination By-products; Some Other Halogenated Compounds; Cobalt and Cobalt Compounds*. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, vol. 52. Lyon, France: International Agency for Research on Cancer. pp. 363-434.
- IARC. 2006. Metallic cobalt particles (with or without tungsten carbide). In *Cobalt in Hard-metals and Cobalt Sulfate, Gallium Arsenide, Indium Phosphide and Vanadium Pentoxide*, IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 86, Lyon, France: International Agency for Research on Cancer. pp. 39-155.
- Jasmin G, Riopelle JL. 1976. Renal carcinomas and erythrocytosis in rats following intrarenal injection of nickel subsulfide. *Lab Invest* 35(1): 71-78.
- Julander A, Lundgren L, Skare L, Grandér M, Palm B, Vahter M, Lidén L. 2014. Formal recycling of e-waste leads to increased exposure to toxic metals: An occupational exposure study from Sweden. *Environ Int* 73: 243-251.
- Kasprzak KS, Zastawny TH, North SL, Riggs CW, Diwan BA, Rice JM, Dizdaroğlu M. 1994. Oxidative DNA base damage in renal, hepatic, and pulmonary chromatin of rats after intraperitoneal injection of cobalt(II) acetate. *Chem Res Toxicol* 7(3): 329-335.
- Kreyling WG, Godleski KJ, Kariya ST, Rose RM, Brain JD. 1990. In vitro dissolution of uniform cobalt oxide particles by human and canine alveolar macrophages. *Am J Respir Cell Mol Biol* 2(5): 413-422.
- Lison D. 2015. Cobalt. In *Handbook on the Toxicology of Metals*, 4th ed., vol. II. Nordberg GF, Fowler BA, Nordberg M, eds. Waltham, MA: Elsevier. pp. 743-763.
- Maverick T. 2015. Cobalt shortage put brakes on electric car. *Wall Street Daily*. <http://www.wallstreetdaily.com/2015/01/13/cobalt-electric-car-battery>.
- Maxwell P, Salnikow K. 2004. HIF-1: An oxygen and metal responsive transcription factor. *Cancer Biol Ther* 3(1): 29-35.
- Mayo Clinic. 2015. *Test ID: COS. Cobalt, serum*. Mayo Medical Laboratories. <http://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/80084>. Last accessed: 4/10/15.
- MHRA. 2012. *Medical Device Alert: All Metal-on-Metal (MoM) Hip Replacements*. MDA/2012/036. Medicines and Healthcare Products Regulatory Agency, National Joint Registry of England, Wales, and Northern Ireland. <https://assets.digital.cabinet-office.gov.uk/media/5485abf6ed915d4c10000273/con155767.pdf>.
- Moulin JJ, Wild P, Mur JM, Fournier-Betz M, Mercier-Gallay M. 1993. A mortality study of cobalt production workers: an extension of the follow-up. *Am J Ind Med* 23(2): 281-288.
- Moulin JJ, Wild P, Romazini S, Lasfargues G, Peltier A, Bozec C, Deguerry P, Pellet F, Perdrix A. 1998. Lung cancer risk in hard-metal workers. *Am J Epidemiol* 148(3): 241-248.
- Moulin JJ, Clavel T, Roy D, Dananché B, Marquis N, Fèveotte J, Fontana JM. 2000. Risk of lung cancer in workers producing stainless steel and metallic alloys. *Int Arch Occup Environ Health* 73(3): 171-180.
- Mur JM, Moulin JJ, Charruyer-Seinerra MP, Lafitte J. 1987. A cohort mortality study among cobalt and sodium workers in an electrochemical plant. *Am J Ind Med* 11(1): 75-81.
- Neale G. 1990. B12 binding proteins. *Gut* 31(1): 59-63.
- Nilsson K, Jensen BS, Carlsen L. 1985. The migration chemistry of cobalt. *Eur Appl Res Rept - Nucl Sci Technol* 7(1): 23-86.
- NIOSH. 2015. *NIOSH Health Hazard Evaluations*. https://java.epa.gov/oppt_chemical_search and search on cobalt. Last accessed: 7/17/15.
- NTP. 1998. *Toxicology and Carcinogenesis Studies of Cobalt Sulfate Heptahydrate in F344/N Rats and B6C3F₁ Mice (Inhalation Studies)*. NTP Technical Report Series No. 471. Research Triangle Park, NC: National Toxicology Program. 268 pp.
- NTP. 2009. Section 2: Human exposure. In *Report on Carcinogens Background Document for Cobalt-Tungsten Carbide Powders and Hard Metals*. National Toxicology Program. http://ntp.niehs.nih.gov/ntp/roc/twelfth/2010/finalbds/hardmetalsbd20100408_508.pdf. pp. 7-37.
- NTP. 2014. *Toxicology Studies of Cobalt Metal (CAS No. 7440-48-4) in F344/N Rats and B6C3F₁/N Mice and Toxicology and Carcinogenesis Studies of Cobalt Metal in F344/N Rats and B6C3F₁/N Mice (Inhalation Studies)*. Technical Report Series No. 581. NIH Publication No. 14-5932. Research Triangle Park, NC: National Toxicology Program. 308 pp.
- NTP. 2015. Appendix B.2: Exposure. In *Report on Carcinogens Monograph on Cobalt and Cobalt Compounds That Release Cobalt Ions In Vivo*. Research Triangle Park, NC: National Toxicology Program. http://ntp.niehs.nih.gov/ntp/about_ntp/monoperrvw/2015/july/cobalt_finalmonograph_508.pdf. pp. B-2-B-15.
- Nyga A, Hart A, Tetley TD. 2015. Importance of the HIF pathway in cobalt nanoparticle-induced cytotoxicity and inflammation in human macrophages. *Nanotoxicology* 9(7): 905-917.
- O'Rourke MA, Cantwell MM, Abnet CC, Brockman AJ, Murray LJ, Group FS. 2012. Toenail trace element status and risk of Barrett's oesophagus and oesophageal adenocarcinoma: Results from the FINBAR study. *Int J Cancer* 131(8): 1882-1891.

Ortega R, Bresson C, Darolles C, Gautier C, Roudeau S, Perrin L, *et al.* 2014. Low-solubility particles and a Trojan-horse type mechanism of toxicity: The case of cobalt oxide on human lung cells. *Part Fibre Toxicol* 11:14. 18 pp.

Paul SAM, Simons JW, Majeesh NJ. 2004. HIF at the crossroads between ischemia and carcinogenesis. *J Cell Physiol* 200(1): 20-30.

Paustenbach DJ, Tvermoes BE, Unice KM, Finley BL, Kerger BD. 2013. A review of the health hazards posed by cobalt. *Crit Rev Toxicol* 43(4): 316-362.

Pennington JAT, Jones JW. 1987. Molybdenum, nickel, cobalt, vanadium, and strontium in total diets. *J Am Diet Assoc* 87(12): 1644-1650.

Peters K, Unger RE, Gatti AM, Sabbioni E, Tsaryk R, Kirkpatrick CJ. 2007. Metallic nanoparticles exhibit paradoxical effects on oxidative stress and pro-inflammatory response in endothelial cells *in vitro*. *Int J Immunopathol Pharmacol* 20(4): 679-689.

PubChem. 2015. *PubChem Compound*. National Center for Biotechnology Information. <http://www.ncbi.nlm.nih.gov/pccompound> and search on CAS number. Last accessed: 3/24/15.

Richter PA, Bishop EE, Wang J, Swahn MH. 2009. Tobacco smoke exposure and levels of urinary metals in the U.S. youth and adult population: The National Health and Nutrition Examination Survey (NHANES) 1999-2004. *Int J Environ Res Public Health* 6(7): 1930-1946.

Rogers MA, Thomas DB, Davis S, Vaughan TL, Nevissi AE. 1993. A case-control study of element levels and cancer of the upper aerodigestive tract. *Cancer Epidemiol Biomarkers Prev* 2(4): 305-312.

Sabbioni E, Minoia C, Pietra R, Mosconi G, Forni A, Scansetti G. 1994a. Metal determinations in biological specimens of diseased and non-diseased hard metal workers. *Sci Total Environ* 150(1-3): 41-54.

Sabbioni E, Fortaner S, Farina M, Del Torchio R, Petrarca C, Bernardini G, *et al.* 2014. Interaction with culture medium components, cellular uptake and intracellular distribution of cobalt nanoparticles, microparticles and ions in Balb/3T3 mouse fibroblasts. *Nanotoxicology* 8(1): 88-99.

Saini Y, Greenwood KK, Merrill C, Kim KY, Patial S, Parameswaran N, Harkema JR, LaPres JJ. 2010a. Acute cobalt-induced lung injury and the role of hypoxia-inducible factor 1 α in modulating inflammation. *Toxicol Sci* 116(2): 673-681.

Saini Y, Kim KY, Lewandowski R, Bramble LA, Harkema JR, LaPres JJ. 2010b. Role of hypoxia-inducible factor 1 α in modulating cobalt-induced lung inflammation. *Am J Physiol Lung Cell Mol Physiol* 298(2): L139-147.

Sampson B, Hart A. 2012. Clinical usefulness of blood metal measurements to assess the failure of metal-on-metal hip implants. *Ann Clin Biochem* 49(Pt 2): 118-131.

Shabaan AA, Marks V, Lancaster MC, Dufey GN. 1977. Fibrosarcomas induced by cobalt chloride (CoCl₂) in rats. *Lab Anim* 11(1): 43-46.

Shedd KB. 1993. *The Materials Flow of Cobalt in the United States*. Bureau of Mines Information Circular 9350. United States Department of the Interior. <http://pubs.usgs.gov/usbm/cic-9350/cic-9350.pdf>.

Shedd KB. 2014a. Cobalt. In *Mineral Commodity Summaries 2014*. U.S. Geological Survey. <http://minerals.usgs.gov/minerals/pubs/commodity/cobalt/mcs-2014-cobal.pdf>.

Shedd KB. 2014b. *USGS 2012 Minerals Yearbook: Cobalt [Advance Release]*. <http://minerals.usgs.gov/minerals/pubs/commodity/cobalt/myb1-2012-cobal.pdf>.

Shukla SJ, Huang R, Simmons SO, Tice RR, Witt KL, Vanleer D, Ramabhadran R, Austin CP, Xia M. 2012. Profiling environmental chemicals for activity in the antioxidant response element signaling pathway using a high throughput screening approach. *Environ Health Perspect* 120(8): 1150-1156.

Smith LJ, Holmes AL, Kandpal SK, Mason MD, Zheng T, Wise JP, Sr. 2014. The cytotoxicity and genotoxicity of soluble and particulate cobalt in human lung fibroblast cells. *Toxicol Appl Pharmacol* 278(3): 259-265.

Steinhoff D, Mohr U. 1991. On the question of a carcinogenic action of cobalt-containing compounds. *Exp Pathol* 41(4): 169-174.

Stopford W, Turner J, Cappellini D, Brock T. 2003. Bioaccessibility testing of cobalt compounds. *J Environ Monit* 5(4): 675-680.

TRI. 2014a. *TRI Explorer Chemical Report. TRI On-Site and Off-site Reported Disposed of or Otherwise Released (in pounds) for Cobalt and Cobalt Compounds*. U.S. Environmental Protection Agency. <http://www.epa.gov/triexplorer>. Last accessed: 10/14/14.

TRI. 2014b. *TRI Explorer Chemical Report. TRI On-Site and Off-Site Reported Disposed of or Otherwise Released (in pounds), Trend Report for Facilities in All Industries for Cobalt Chemical, U.S.* U.S. Environmental Protection Agency. <http://www.epa.gov/triexplorer>. Last accessed: 10/14/14.

TRI. 2014c. *TRI Explorer Chemical Report. TRI On-site and Off-site Reported Disposed of or Otherwise Released (in pounds), Trend Report for Facilities in All Industries, for Cobalt Compounds Chemical, U.S.* U.S. Environmental Protection Agency. <http://www.epa.gov/triexplorer>. Last accessed: 10/13/14.

Tüchsen F, Jensen MV, Villadsen E, Lyng E. 1996. Incidence of lung cancer among cobalt-exposed women. *Scand J Work Environ Health* 22(6): 444-450.

USITC. 2014. *USITC Interactive Tariff and Trade Databe*. United States International Trade Commission. http://databe.usitc.gov/scripts/user_set.asp and search on HTS nos. 2836999050, 2836991000, 2833291000, 2833299100, 8105200000, 8105209000, 8105203000, 8105206000, 2836991000, 2833291000, 8105209000, 8105203000, 8105900000, 2915293000, 2827396000, 2605000000, 2822000000, 8105300000. Last accessed: 10/14.

Valko M, Morris H, Cronin MT. 2005. Metals, toxicity and oxidative stress. *Curr Med Chem* 12(10): 1161-1208.

Valko M, Rhodes CJ, Moncol J, Izakovic M, Mazur M. 2006. Free radicals, metals and antioxidants in oxidative stress-induced cancer. *Chem Biol Interact* 160(1): 1-40.

Wehner AP, Busch RH, Olson RJ, Craig DK. 1977. Chronic inhalation of cobalt oxide and cigarette smoke by hamsters. *Am Ind Hyg Assoc J* 38(7): 338-346.

WHO. 2006. *Cobalt and Inorganic Cobalt Compounds*. Concise International Chemical Assessment Document 69. International Programme on Chemical Safety. <http://www.inchem.org/documents/cicads/cicads/cicad69.htm>.

Wild P, Perdrix A, Romazini S, Moulin JJ, Pellet F. 2000. Lung cancer mortality in a site producing hard metals. *Occup Environ Med* 57(8): 568-573.

Cobalt–Tungsten Carbide: Powders and Hard Metals

CAS No.: none assigned

Reasonably anticipated to be a human carcinogen

First listed in the *Twelfth Report on Carcinogens* (2011)

Also known as Co/WC, WC/Co

Carcinogenicity

Cobalt–tungsten carbide powders and hard metals are *reasonably anticipated to be human carcinogens* based on limited evidence of carcinogenicity from studies in humans and supporting evidence from studies on mechanisms of carcinogenesis.

Cancer Studies in Humans

Epidemiological studies provide evidence for the carcinogenicity of cobalt–tungsten carbide powders and hard metals based on (1) consistent findings of excess lung-cancer mortality among cobalt–tungsten carbide hard-metal manufacturing workers across studies, (2) higher risks among individuals with higher exposure levels, and (3) positive exposure-response relationships that cannot be explained by confounding with tobacco smoking. However, the epidemiological data are limited, because there are few studies of independent populations.

The published epidemiological literature consists of mortality studies of two independent multi-plant cohorts of cobalt–tungsten carbide hard-metal manufacturing workers, one in France (Moulin *et al.* 1998) and one in Sweden (Hogstedt and Alexandersson 1990), and cohort studies of two individual factories included in the French multi-plant cohort (Lasfargues *et al.* 1994, Wild *et al.* 2000). The French multi-plant cohort included all 10 cobalt–tungsten carbide manufacturing plants in France; in addition, a nested case-control study of lung cancer was conducted within this cohort. The nested case-control study is most informative for evaluating cancer risk, because it used a semi-quantitative exposure scale to evaluate exposure-response relationships and considered potential confounding by exposure to tobacco smoking and other known or suspected occupational carcinogens. The cohort study of the largest French factory shares these advantages; however, because the workers were included in the multi-plant study, it does not provide independent evidence for carcinogenicity. In these two studies, four metrics of exposure were evaluated: (1) exposure level, which was the highest exposure score experienced during an individual's work history (on a scale of 0 to 9), (2) duration of exposure at a level of 2 or higher, (3) unweighted cumulative dose, which assigned the same level to occasional and full-time exposure, thus favoring peak exposure, and (4) frequency-weighted cumulative dose, which weighted exposure level by the frequency of exposure, thus reducing the effect of occasional exposure. The Swedish study, although limited in size, provides supporting information for an independent population.

Excess lung-cancer mortality (of approximately 30%) was found in both multi-plant cohort studies (Hogstedt and Alexandersson 1990, Moulin *et al.* 1998); risk estimates were significantly higher among individuals with higher measures of exposure or longer time since first exposure (latency). In the nested case-control study (Moulin *et*

al. 1998), lung cancer risk was significantly higher (odds ratio [OR] = 1.93, 95% CI = 1.03 to 3.62, 35 exposed cases) among workers exposed to cobalt–tungsten carbide (exposure level ≥ 2) than among workers with little or no exposure (exposure level < 2). In exposure-response analyses using workers in the lowest exposure category as the comparison group, lung-cancer risk was significantly higher (by up to fourfold) for workers in the highest categories of both measures of cumulative dose, and an elevated risk of borderline statistical significance was found for workers in the highest exposure-level category. Positive exposure-response relationships were observed for all four measures of exposure: duration ($P_{\text{trend}} = 0.03$), unweighted cumulative dose ($P_{\text{trend}} = 0.01$), frequency-weighted cumulative dose ($P_{\text{trend}} = 0.08$), and exposure level ($P_{\text{trend}} = 0.08$). Adjustment for tobacco smoking or exposure to known or suspected carcinogens did not change the results. The Swedish study had limited ability to evaluate exposure-response relationships because of small numbers of exposed workers with lung cancer. Nevertheless, the risk of lung cancer mortality was significantly increased for workers with exposure duration of over 10 years and latency of over 20 years (standardized mortality ratio [SMR] = 2.78, 95% CI = 1.11 to 5.72, 7 exposed cases). Analyses restricted to workers with at least 10 years' exposure or at least 20 years' latency found somewhat higher SMRs for "high-exposed" than "low-exposed" workers (Hogstedt and Alexandersson 1990).

Excess risks of lung-cancer mortality were also found in studies of the two individual French factories. Wild *et al.* (2000) reported significantly elevated SMRs (by approximately twofold) for lung cancer among all male workers and among male workers ever employed in presintering workshops or with exposure levels of at least 2. The highest SMRs were observed for male workers in the highest exposure categories of all four exposure metrics (level, duration, and both measures of cumulative dose), although the trends were not statistically significant, and the risk estimates were imprecise. In the study by Lasfargues *et al.* (1994), the entire cohort had a significantly increased risk of lung cancer, and the risk was highest among workers in the highest exposure-level category. Although small, this study provides supporting evidence that the findings for the French industry-wide cohort were not due solely to the results for the large factory studied by Wild *et al.*

Both the French multi-plant cohort study (Moulin *et al.* 1988) and the larger study of an individual French factory (Wild *et al.* 2000) found higher risks of lung cancer for exposure to cobalt–tungsten carbide before sintering than after sintering (see Production). The authors stated that exposure was highest during presintering processes; however, there is no evidence of toxicological differences between presintered and sintered materials, and both materials release similar amounts of cobalt ions (see Studies on Mechanisms of Carcinogenesis).

It is unlikely that the excess risks of lung cancer found in the French studies were due to confounding by tobacco smoking or co-exposure to other known carcinogens. In the multi-plant study, the smoking-adjusted odds ratio for cobalt–tungsten carbide exposure (OR = 2.6, 95% CI = 1.16 to 5.82) was similar to the unadjusted risk (OR = 2.29, 95% CI = 1.08 to 4.88). Neither study found increased risks of smoking-related diseases, such as chronic bronchitis and emphysema, and adjustment for smoking or exposure to other occupational carcinogens did not change the findings in the exposure-response analyses (Moulin *et al.* 1988, Wild *et al.* 2000). Neither the Swedish multi-plant study (Hogstedt and Alexandersson 1990) nor the small French cohort study (Lasfargues *et al.* 1994) adjusted for smoking; however, surveys of smoking habits among a subset of workers found smoking rates similar to those in the general population. Overall, the studies are limited by the lack of quantitative exposure as-

essment and potential confounding; however, exposure misclassification would most likely reduce the likelihood of detecting a true effect.

Studies on Mechanisms of Carcinogenesis

The findings from epidemiological studies are supported by studies on mechanisms of carcinogenesis. Although the mechanism(s) by which cobalt–tungsten carbide causes cancer have not been fully elucidated, it has been shown that (1) cobalt–tungsten carbide releases cobalt ions, (2) cobalt ions affect biochemical pathways related to carcinogenicity, (3) cobalt compounds are carcinogenic in experimental animals, (4) cobalt–tungsten carbide increases the production of reactive oxygen species (ROS) and causes greater cytotoxic, toxic, and genotoxic effects than does cobalt alone, (5) cobalt–tungsten carbide causes key events related to carcinogenesis, including genotoxicity, cytotoxicity, inflammation, and apoptosis (programmed cell death), and (6) the oxidative stress response resulting from increased ROS production may play a role in these key events and may also interfere with cells' ability to repair damage caused by cobalt–tungsten carbide. The combination of the effects from cobalt ions and the oxidative stress response from ROS production provide plausible modes of action for the carcinogenicity of cobalt–tungsten carbide.

Studies in biological fluids, *in vitro* systems, experimental animals, and humans have demonstrated that cobalt is rapidly solubilized from cobalt–tungsten carbide. Cobalt dissolution rates were similar for presintered and sintered cobalt–tungsten carbide incubated in various artificial biological fluids (Stopford *et al.* 2003). Tungsten is not rapidly solubilized from cobalt–tungsten carbide, but can be phagocytized by macrophages (Lombaert *et al.* 2004). Cobalt was also released from hard-metal dust incubated with plasma and lung tissue (Edel *et al.* 1990). In experimental animals administered cobalt–tungsten carbide by intratracheal administration, cobalt was solubilized rapidly, cleared from the lung, distributed in the body, and excreted in the urine (Lison 1996). Rats exposed intratracheally to cobalt–tungsten carbide had more cobalt in the urine than did rats administered cobalt alone, suggesting that tungsten carbide increases the bioavailability of cobalt (Lasfargues *et al.* 1992). Several biomonitoring studies detected elevated levels of cobalt in the urine, lungs, and other tissues of workers exposed to cobalt–tungsten carbide hard metals (Rizzato *et al.* 1986, Nicolaou *et al.* 1987, Gallorini *et al.* 1994, Sabbioni *et al.* 1994b, Scansetti *et al.* 1994, 1998, Linnainmaa and Kiilunen 1997, Goldoni *et al.* 2004).

Soluble cobalt compounds are genotoxic and carcinogenic in experimental animals. Cobalt and cobalt compounds that release cobalt ions *in vivo* are listed as *reasonably anticipated to be human carcinogens* in the Report on Carcinogens based on sufficient evidence of carcinogenicity from studies of cobalt metal, cobalt sulfate, cobalt chloride, and cobalt oxide in experimental animals and supporting evidence from studies on mechanisms of carcinogenesis. Cobalt ions produce ROS, which cause oxidative DNA damage and act on a number of cancer-related molecular targets. Cobalt ions disrupt cell-signaling pathways (Murata *et al.* 1999), inhibit DNA repair (Hartwig 2000, Hartwig *et al.* 2002), regulate genes involved in the response to hypoxia (Beyersmann 2002), replace or mimic essential divalent metal ions, thus altering cellular reactions (Nackerdien *et al.* 1991, Beyersmann and Hartwig 1992, Kawanishi *et al.* 1994, Lloyd *et al.* 1998), and interfere with mechanisms involved in cell-cycle control and modulation of apoptosis (DeBoeck *et al.* 2003b,c).

Numerous *in vitro* studies (reviewed in NTP 2009) and *in vivo* studies (Huaux *et al.* 1995, Lasfargues *et al.* 1995) have shown greater cytotoxic effects (measured primarily by lactate dehydrogenase release) for cobalt–tungsten carbide than for either cobalt powder or tungsten carbide alone. The mixture's greater *in vitro* toxicity to

macrophages is not fully explained by greater bioavailability of cobalt (Lison and Lauwerys 1992, 1994). Respirable samples collected at various stages of the hard-metal manufacturing process (including powders for pressing, presintered materials, and powders from grinding of sintered materials) caused cytotoxicity and pathological changes in the lungs of rats after intratracheal injection (Adamis *et al.* 1997). In addition, cobalt–tungsten carbide causes a type of respiratory toxicity (“hard-metal disease”) that is not observed with exposure to cobalt alone. Hard-metal disease is characterized by a giant-cell interstitial pneumonia that can develop into lung fibrosis (Lison 1996, Lison *et al.* 1996).

There is some evidence that the greater toxicity of cobalt–tungsten carbide may result from a physicochemical reaction that takes place at the interface between certain carbides and cobalt particles (Lison and Lauwerys 1992). The structural features of the two particles may help to explain the effects. Cobalt metal can reduce ambient oxygen, but only at a low rate of reaction, because of the particles’ surface characteristics. Tungsten carbide is inert and does not react with oxygen but is a good electron conductor. When cobalt and tungsten carbide particles are associated, the cobalt electrons are transferred to the carbide surface, allowing increased oxygen reduction and thus increased production of ROS. Biochemical studies on the production of ROS have shown that cobalt’s capacity to generate hydroxyl radicals is greatly increased by association with tungsten carbide. Formation of the ROS results directly from the interaction of cobalt with tungsten carbide or indirectly from the cobalt ions generated from the Fenton-like reaction of the cobalt metal with the carbide (Lison and Lauwerys 1993, Lison *et al.* 1995). In oxygen-radical-generating systems, post-sintered powders sampled from final machining (grinding) of cobalt–tungsten carbide products produced higher levels of ROS than did pre-sintered samples of cobalt and tungsten carbide separately or as mixtures (Stefaniak *et al.* 2010).

Metal-induced generation of ROS in cellular test systems leads to oxidative stress as a result of increased free radicals and insufficient antioxidative defense. Protective mechanisms include cellular antioxidant systems, the stress-protein response, and the involvement of DNA excision and repair enzymes (Kasten *et al.* 1997, Shi *et al.* 2004, Lombaert *et al.* 2008). Fenoglio *et al.* (2008) studied oxidation of the antioxidant glutathione and cysteine sulfhydryl groups by cobalt–tungsten carbide dust–induced ROS and reported dust-concentration-dependent generation of thiyl radicals at particle surface sites. Depletion of cellular antioxidant defenses could further exacerbate cellular oxidative damage caused by ROS generated by cobalt–tungsten carbide particles.

Regulation of gene expression, including apoptotic, stress-protein, and immune-response pathways, also can be affected by ROS. Lombaert *et al.* (2008) evaluated the effects of cobalt–tungsten carbide exposure *in vitro* on patterns of gene expression in human peripheral-blood mononucleated cells and reported statistically significant up-regulation of apoptosis and stress or defense response pathways and down-regulation of immune-response pathways.

Apoptosis has been associated with exposure to a number of known carcinogens (arsenic, cadmium, chromium, nickel, and beryllium) and possible carcinogens (cobalt and lead). Cobalt chloride has been shown to induce apoptosis through formation of ROS in both human alveolar macrophages and a rat pheochromocytoma cell line (PC12); co-administration of antioxidants suppressed ROS production and restored cell viability (Zou *et al.* 2001, Araya *et al.* 2002). Cobalt–tungsten carbide, tungsten carbide, and cobalt ions induced apoptosis in human lymphocytes; the effect of the mixture was significantly greater than that of tungsten carbide or cobalt alone (Lombaert *et al.* 2004).

Cobalt–tungsten carbide is genotoxic *in vitro* and causes mutations in the lungs of rats exposed *in vivo*. Its genotoxicity (clastogenic effects) may be caused by increased ROS production from the interaction between cobalt and tungsten carbide, from ionic cobalt, or from both. In addition, cobalt ions inhibit DNA repair, which may also contribute to cobalt–tungsten carbide’s genotoxic effects. Specifically, cobalt–tungsten carbide caused DNA strand breaks in mouse 3T3 fibroblasts and human peripheral-blood lymphocytes (Anard *et al.* 1997) and micronucleus formation in human peripheral-blood lymphocytes (Van Goethem *et al.* 1997, De Boeck *et al.* 2003c). In these studies, cobalt–tungsten carbide was more genotoxic than cobalt alone. In rats exposed by intratracheal instillation, cobalt–tungsten carbide caused DNA damage and micronucleus formation in the lung (type II pneumocytes) (De Boeck *et al.* 2003a). No increase in DNA damage or micronucleus formation was observed in rat peripheral-blood lymphocytes; however, it is unclear whether circulating lymphocytes are a good reporter for monitoring genotoxic effects from inhaled particles. In humans, neither DNA damage nor micronucleus formation was increased in lymphocytes of cobalt–tungsten carbide hard-metal workers, compared with unexposed workers; however, this study was limited by small sample size (De Boeck *et al.* 2000). Multiple regression analyses (Mateuca *et al.* 2005) indicated that both end points were associated with an interaction between tobacco smoking and exposure, and that micronucleus formation was associated with smoking, working in a cobalt–tungsten carbide plant, and having variant forms of genes coding for DNA repair enzymes (X-ray repair cross-complementing group 3 and 8-oxoguanine DNA glycosylase).

In addition, although the pathogenesis of hard-metal disease is not fully understood, it may involve differences in the susceptibility (genetic and/or health-related) of affected individuals to the toxic effects of increased ROS production due to cobalt–tungsten carbide exposure. Further, the mechanisms for fibrosing alveolitis and lung cancer in hard-metal workers may be related, conceivably involving oxidative damage and/or inflammatory events (IARC 2006).

Cancer Studies in Experimental Animals

No studies in experimental animals were identified that evaluated the relationship between cancer and exposure specifically to cobalt–tungsten carbide powders or hard metals.

Properties

This listing includes powders and dusts (either unsintered or sintered) containing both cobalt and tungsten carbide and hard metals containing both cobalt and tungsten carbide. Powders containing both cobalt and tungsten carbide may result from combination of these materials during manufacture of hard metals, and dusts containing both materials may result from production, finishing, or maintenance (e.g., sharpening or grinding) of cobalt–tungsten carbide hard-metal products. Cobalt–tungsten carbide hard metals are composites of tungsten carbide particles (either alone or in combination with smaller amounts of other carbides) with a metallic cobalt powder as a binder, pressed into a compact, solid form at high temperatures by a process known as “sintering.” Cobalt–tungsten carbide hard metals are commonly referred to as “cemented carbides” in the United States, but the term “sintered carbide” also may be used, and some sources refer to cobalt–tungsten carbide products simply as “tungsten carbides” (Brookes 2002).

The physical properties of cobalt–tungsten carbide hard metals vary with the relative proportions of cobalt, tungsten carbide, and other carbides, but they have common properties of extreme hardness, abrasion resistance, and toughness. Tungsten carbide is hard (able

to resist cutting, abrasion, penetration, bending, and stretching) but brittle; cobalt is soft but tough (able to withstand great strain without tearing or breaking). The composition of commercial-grade cobalt–tungsten carbide hard metals can vary greatly; it generally ranges from 50% to 97% tungsten carbide (along with other metallic carbides such as titanium carbide or tantalum carbide) and from 3% to 16% cobalt, with variations in grain size and additives. The proportion of cobalt as the binding metal in the composite hard metal depends on the intended use (Azom 2002). Cobalt–tungsten carbide hard metals for various uses have Vickers hardness values (a measure of the resistance of a substance to indentation by a diamond penetrator of special profile) typically ranging from 1250 to 1900 (Brookes 1998).

The crystalline structure of cobalt–tungsten carbide includes the structures individually of cobalt, which can exist as either hexagonal or cubic crystals, and tungsten carbide, which consists primarily of W_2C , WC , and possibly other carbides (Upadhyaya 1998b). The phase diagram for the combination of cobalt and tungsten carbide is extremely complex, as tungsten can form a solid solution in cobalt, and cobalt can form carbides with carbon; the overall relationship varies with the concentrations of the major components and the temperature.

Mixtures of cobalt and tungsten carbide are more active than the individual components in adsorption of water vapor (with respect to both the amount adsorbed and the interaction energy) and in the catalytic decomposition of hydrogen peroxide (Zanetti and Fubini 1997). Physical and chemical properties of tungsten carbide and cobalt are listed in the following table.

Property	Cobalt	Tungsten carbide
Molecular or atomic weight	58.9	195.9
Density	8.92	15.6
Melting point	1,495°C	2,785°C
Boiling point	2,927°C	6,000°C
Vapor pressure	1 Pa at 1,517°C (0.0075 mmHg)	NR

Source: HSDB 2010. NR = not reported.

Use

About 70% of cobalt–tungsten carbide hard-metal production is used for cutting tools and 30% for wear-resistant materials, primarily for tools for mining and grinding operations (Santhanam 2003). Hard-metal grades for machining are assigned International Organization for Standardization (ISO) codes beginning with “P” for machining of steel, “M” for multiple purposes, including machining of steel, nickel-based superalloys, and higher-tensile-strength (ductile) cast iron, and “K” for cutting of lower-tensile strength (gray) cast iron, nonferrous metals, and nonmetallic materials.

Production

Cobalt–tungsten carbide hard metals were developed in Germany during and after World War I and marketed commercially by a German company in 1927 as Widia, which consisted of tungsten carbide with 6% cobalt as binder (Brookes 1998, Upadhyaya 1998a). Cobalt–tungsten carbide hard-metal manufacturing processes vary somewhat, but all involve production of cobalt and tungsten carbide powders, which are mixed, pressed into a compact, solid form, and sintered by heating to about 1,500°C. The manufacturing process consists of three steps: Step 1, producing the cobalt and tungsten carbide powders; Step 2, mixing, drying, pressing, presintering, shaping the presintered hard metal, and sintering; and Step 3, finishing the sintered products, which includes grinding and sharpening.

Worldwide use of cemented carbides has increased steadily over the years, from about 10 tons in 1930 to 30,000 tons per year in the

early 2000s (Azom 2002). In 2004, estimated U.S. production of hard-metal products totaled 5,527 metric tons (6,080 tons) (Hsu 2004). The U.S. Geological Survey (USGS 2008a,b) estimated that 792 metric tons (873 tons) of cobalt (9.3% of total U.S. cobalt consumption) and 6,610 metric tons (7,286 tons) of tungsten (56% of total U.S. tungsten consumption) was used in the production of cemented carbides in the United States in 2007. In 2008, 127 U.S. and Canadian companies were identified that produced or supplied cobalt–tungsten carbide and materials made from cobalt–tungsten carbide (Thomas-Net 2008), and the Cemented Carbide Producers Association had 22 U.S. members and partner members (CCPA 2008). In 2007, the United States imported about 1.6 million kilograms (1,800 tons) and exported about 1.3 million kilograms (1,400 tons) of tungsten carbide (USITC 2008); no data specific to U.S. imports or exports of cobalt–tungsten carbide were found.

Exposure

The major source of exposure to cobalt–tungsten carbide powders and hard metals is occupational. However, people who live in the vicinity of hard-metal production or maintenance facilities could be exposed to cobalt–tungsten carbide hard-metal dusts. Although no exposure levels for the general population were found, some studies provided data on possible environmental contamination from the manufacture or maintenance of hard-metal products. Soil sampled from the rear of a cemented carbide tool-grinding plant contained cobalt at concentrations of up to 12,780 mg/kg (Abraham and Hunt 1995). The concentrations of tungsten and cobalt in airborne particulates in Fallon, Nevada, and four nearby towns were characterized by Sheppard *et al.* (2006), who found higher levels of tungsten (0.1 to 40.9 ng/m³) and cobalt (0.02 to 0.16 ng/m³) in Fallon than in the other towns. The authors suggested that a hard-metal facility located in Fallon could be a candidate source for airborne exposure to the metals, a suggestion that has been disputed (see NTP 2009).

Sources of occupational exposure to cobalt–tungsten carbide during the manufacture of hard metals include the processes of mixing, drying, pressing, presintering, shaping, and sintering (parts of Step 2, as described under Production) and the processes of grinding and sharpening sintered products (parts of Step 3, as described under Production). Exposure to cobalt–tungsten carbide hard metals can also occur from other miscellaneous manufacturing operations, during processing of hard-metal scrap for recycling, and during end use and maintenance of hard-metal tools. Particle size (and hence respirable fraction), morphology, and concentrations of airborne dusts and bulk dusts were found to differ among production areas (Stefaniak *et al.* 2007). For cobalt-containing particles, the minimum mass median aerodynamic diameter (MMAD) was 6 μ m (for dry grinding), and the maximum MMAD was over 18 μ m (for scrap reclamation and pressing operations); the MMAD for powder mixing was around 10 μ m, which is generally considered the maximum diameter for respirable particles in humans. Inhalable, thoracic, and respirable particles were found in all work areas of three facilities that together carried out the cobalt–tungsten carbide manufacturing process, with the highest levels reported for the powder-mixing area (Stefaniak *et al.* 2009). Cobalt and tungsten have been detected in workers’ urine, blood, hair, toenails, and bronchoalveolar lavage fluid, and through open lung and transbronchial biopsy (NTP 2009).

Step 2 processes, particularly powder-processing operations, generally are associated with the highest airborne exposures; several studies reported cobalt concentrations approaching or exceeding 5,000 μ g/m³ (NTP 2009). A maximum mean cobalt air concentration of 32,740 μ g/m³ (range = 44 to 438,000 μ g/m³) was reported during weighing and mixing operations in a U.S. manufacturing facility

(Sprince *et al.* 1984). An Italian study reported a mean tungsten air concentration of 26 $\mu\text{g}/\text{m}^3$ (Sabbioni *et al.* 1994a), and a German study reported a maximum single measurement of 254 $\mu\text{g}/\text{m}^3$ (Kraus *et al.* 2001). Among workers involved in Step 2 manufacturing processes, cobalt was detected in the urine (at up to 2,100 $\mu\text{g}/\text{L}$), blood or serum (at up to 32 $\mu\text{g}/\text{L}$), and hair (at up to 25.8 ppm), and tungsten was detected in urine (at up to 169 $\mu\text{g}/\text{L}$).

Cobalt air concentrations reported for Step 3 processes (including tool finishing, grinding, and reconditioning operations) have generally been lower than those for Step 2, but have exceeded 1,000 $\mu\text{g}/\text{m}^3$ in some studies (NTP 2009). For Step 3 processes, a maximum mean cobalt air concentration of 1,292 $\mu\text{g}/\text{m}^3$ and a maximum single measurement of 2,440 $\mu\text{g}/\text{m}^3$ were reported, both for dry-grinding operations. For tungsten in air, a maximum mean concentration of 5,160 $\mu\text{g}/\text{m}^3$ and a maximum single measurement of 12,800 $\mu\text{g}/\text{m}^3$ were reported. Among workers involved specifically in Step 3 processes, cobalt was detected in urine (at up to 730 $\mu\text{g}/\text{L}$), blood (at up to 39 $\mu\text{g}/\text{L}$), and hair (at up to 9.11 ppm). Tungsten also was detected in urine (at up to 1,000 $\mu\text{g}/\text{L}$) and blood (at up to 60 $\mu\text{g}/\text{L}$).

A few studies reported on exposure for jobs outside of the cobalt-tungsten carbide production process. McDermott (1971) reported airborne cobalt concentrations during packing operations (10 to 250 $\mu\text{g}/\text{m}^3$), equipment cleaning (40 to 820 $\mu\text{g}/\text{m}^3$), and miscellaneous operations (10 to 6,700 $\mu\text{g}/\text{m}^3$), but the nature of these operations was not defined further. Maintenance activities (including housekeeping) were reported by Scansetti *et al.* (1985) to result in airborne cobalt concentrations exceeding 50 $\mu\text{g}/\text{m}^3$, and Kraus *et al.* (2001) reported urinary levels associated with maintenance activities ranging from 1.3 to 4.7 $\mu\text{g}/\text{L}$ for cobalt and 1.5 to 5.3 $\mu\text{g}/\text{L}$ for tungsten.

Information on exposure from the end use of hard-metal tools is limited; however, exposure appears to be minimal. Pellet *et al.* (1984) reported cobalt air concentrations of 180 to 193 $\mu\text{g}/\text{m}^3$ and a mean urinary cobalt concentration of 11.7 $\mu\text{g}/\text{L}$ associated with use of hard metal; however, no additional information was provided for these data. No other information was found that directly demonstrated exposure to cobalt-tungsten carbide powders and hard metals by end users of products containing the material. The Washington State Department of Labor, in a Hazard Alert issued in March 1995, stated that there was no evidence of substantial exposure to cobalt during the use of tools containing tungsten carbide or other hard metals (WSDLI 1995).

Several studies found significant correlations between cobalt concentrations in air and in workers' blood or urine (Ichikawa *et al.* 1985, Scansetti *et al.* 1985, Lison *et al.* 1994, Sabbioni *et al.* 1994b). Urinary cobalt levels for hard-metal workers have been reported to increase through the workday (Torra *et al.* 2005) and workweek (Lison *et al.* 1994, Scansetti *et al.* 1998, Torra *et al.* 2005). In one study, urinary cobalt concentrations were significantly higher ($P < 0.005$) at the end of a shift than at the beginning of the shift, with significant increases "day in and day out" during the workweek (Torra *et al.* 2005).

Regulations

U.S. Environmental Protection Agency (EPA)

Clean Water Act

Tungsten and cobalt discharge limits are imposed for numerous processes during the production of tungsten or cobalt at secondary tungsten and cobalt facilities processing tungsten or tungsten carbide scrap raw materials.

Discharge limits for tungsten are imposed for numerous processes during the production of tungsten at primary tungsten facilities.

Discharge limits for cobalt are imposed for numerous processes during the production of cobalt at primary cobalt facilities.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Cobalt and cobalt compounds are listed substances subject to reporting requirements.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers. Permissible exposure limits (PEL) (8-h TWA) = 0.1 mg/m³ for cobalt metal, dust, and fume (as Co); = 5 mg/m³ for insoluble tungsten compounds (as W).

Short-term exposure limits (STEL) = 10 mg/m³ for insoluble tungsten compounds (as W).

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.02 mg/m³ for cobalt and inorganic cobalt compounds; = 5 mg/m³ for tungsten metal and insoluble compounds.

Threshold limit value – short-term exposure limit (TLV-STEL) = 10 mg/m³ for tungsten metal and insoluble compounds.

Biological exposure index (BEI) (end of shift at end of workweek) = 15 $\mu\text{g}/\text{L}$ for cobalt in urine.

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (REL) (10-h TWA) = 0.05 mg/m³ for cemented tungsten carbide containing > 2% Co (as Co); = 0.05 mg/m³ for cobalt metal dust and fume (as Co); = 5 mg/m³ for tungsten and insoluble tungsten compounds (as W).

Immediately dangerous to life and health (IDLH) limit = 20 mg/m³ for cobalt metal dust and fume (as Co).

Short-term exposure limit (STEL) = 10 mg/m³ for tungsten and insoluble tungsten compounds (as W).

References

- Abraham JL, Hunt A. 1995. Environmental contamination by cobalt in the vicinity of a cemented tungsten carbide tool grinding plant. *Environ Res* 69(1): 67-74.
- Adamis Z, Tatnai E, Honma K, Karpati J, Ungvary G. 1997. A study on lung toxicity of respirable hard metal dusts in rats. *Ann Occup Hyg* 41(5): 515-526.
- Anard D, Kirsch-Volders M, Elhajoui A, Belpaeme K, Lison D. 1997. *In vitro* genotoxic effects of hard metal particles assessed by alkaline single cell gel and elution assays. *Carcinogenesis* 18(1): 177-184.
- Angerer J, Heinrich R. 1988. Chapter 20: Cobalt. In *Handbook on Toxicity of Inorganic Compounds*. Seiler HG, Sigel H, eds. New York: Marcel Dekker. pp. 251-264.
- Araya J, Maruyama M, Inoue A, Fujita T, Kawahara J, Sassa K, *et al.* 2002. Inhibition of proteasome activity is involved in cobalt-induced apoptosis of human alveolar macrophages. *Am J Physiol Lung Cell Mol Physiol* 283(4): L849-L858.
- Azom. 2002. *Tungsten Carbide — An Overview*. The A to Z of Materials. <http://www.azom.com/Details.asp?ArticleID=1203>.
- Beyersmann D, Hartwig A. 1992. The genetic toxicology of cobalt. *Toxicol Appl Pharmacol* 115(1): 137-145.
- Beyersmann D. 2002. Effects of carcinogenic metals on gene expression. *Toxicol Lett* 127(1-3): 63-68.
- Brookes K. 2002. Through the looking glass—the rather odd world of hardmetals. *Metal Powder Report* 57(5): 28-29.
- Brookes KJA. 1998. *Hardmetals and Other Hard Materials*, 3rd ed. East Barnet, Hertfordshire, England: International Carbide Data. 220 pp.
- CCPA. 2008. *Cemented Carbide Producers Association — Members*. Cemented Carbide Producers Association. <http://www.ccpa.org/pages/members.html>. Last accessed: 10/6/08.
- De Boeck M, Lardau S, Buchet JP, Kirsch-Volders M, Lison D. 2000. Absence of significant genotoxicity in lymphocytes and urine from workers exposed to moderate levels of cobalt-containing dust: a cross-sectional study. *Environ Mol Mutagen* 36(2): 151-160.
- De Boeck M, Hoet P, Lombaert N, Nemery B, Kirsch-Volders M, Lison D. 2003a. *In vivo* genotoxicity of hard metal dust: induction of micronuclei in rat type II epithelial lung cells. *Carcinogenesis* 24(11): 1793-1800.
- De Boeck M, Kirsch-Volders M, Lison D. 2003b. Cobalt and antimony: Genotoxicity and carcinogenicity. *Mutat Res* 533(1-2): 135-152.
- De Boeck M, Lombaert N, De Backer S, Finsy R, Lison D, Kirsch-Volders M. 2003c. *In vitro* genotoxic effects of different combinations of cobalt and metallic carbide particles. *Mutagenesis* 18(2): 177-186.
- De Boeck M, Kirsch-Volders M, Lison D. 2004. Corrigendum to "Cobalt and antimony: genotoxicity and carcinogenicity" [Mutat Res 533 (2003) 135-152]. *Mutat Res* 548(1-2): 127-128.
- Edel J, Sabbioni E, Pietra R, Rossi A, Torre M, Rizzato G, Fraioli P. 1990. Trace metal lung disease: *In vitro* interaction of hard metals with human lung and plasma components. *Sci Total Environ* 95: 107-117.
- Fenoglio I, Corazzari I, Francia C, Bodoardo S, Fubini B. 2008. The oxidation of glutathione by cobalt/tungsten carbide contributes to hard metal-induced oxidative stress. *Free Radic Res* 42(8): 737-745.
- Gallorini M, Edel J, Pietra R, Sabbioni E, Mosconi G. 1994. Cobalt speciation in urine of hard metal workers — a study carried out by nuclear and radioanalytical techniques. *Sci Total Environ* 150(1-3): 153-160.
- Goldoni M, Catalani S, De Palma G, Manini P, Acampa O, Corradi M, Bergonzi R, Apostoli P, Mutti A. 2004. Exhaled breath condensate as a suitable matrix to assess lung dose and effects in workers. *Environ Health Perspect* 112(13): 1293-1298.
- Hartwig A. 2000. Recent advances in metal carcinogenicity. *Pure Appl Chem* 72(6): 1007-1014.

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For definitions of technical terms, see the [Glossary](#).

- Hartwig A, Asmuss M, Ehleben I, Herzer U, Kostelac D, Pelzer A, Schwerdtle T, Bürkle A. 2002. Interference by toxic metal ions with DNA repair processes and cell cycle control: molecular mechanisms. *Environ Health Perspect* 110(Suppl 5): 797-799.
- Hogstedt C, Alexandersson R. 1990. Dödsorsaker hos Hardmetallarbetare. *Arbete och Hälsa* 21: 1-26.
- HSDB. 2010. *Hazardous Substances Data Bank*. National Library of Medicine. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB> and search on cobalt, elemental; and search on tungsten carbide. Last accessed: 4/15/10.
- Hsu WY. 2004. Hsu WY, Kennametal, Inc., Latrobe, PA, letter to Jameson CW, National Toxicology Program, Research Triangle Park, NC, July 16, 2004.
- Huax F, Lasfargues G, Lauwerys R, Lison D. 1995. Lung toxicity of hard metal particles and production of interleukin-1, tumor necrosis factor-alpha, fibronectin, and cystatin-c by lung phagocytes. *Toxicol Appl Pharmacol* 132(1): 53-62.
- IARC. 2006. *Cobalt in Hard-metals and Cobalt Sulfate, Gallium Arsenide, Indium Phosphide and Vanadium Pentoxide*, IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 86, Lyon, France: International Agency for Research on Cancer. 330 pp.
- Ichikawa Y, Kusaka Y, Goto S. 1985. Biological monitoring of cobalt exposure, based on cobalt concentrations in blood and urine. *Int Arch Occup Environ Health* 55(4): 269-276.
- Kasten U, Mullenders LH, Hartwig A. 1997. Cobalt(II) inhibits the incision and the polymerization step of nucleotide excision repair in human fibroblasts. *Mutat Res* 383(1): 81-89.
- Kawanishi S, Inoue S, Yamamoto K. 1994. Active oxygen species in DNA damage induced by carcinogenic metal compounds. *Environ Health Perspect* 102(Suppl 3): 17-20.
- Kraus T, Schramel P, Schaller KH, Zöbele P, Weber A, Angerer J. 2001. Exposure assessment in the hard metal manufacturing industry with special regard to tungsten and its compounds. *Occup Environ Med* 58(10): 631-634.
- Lasfargues G, Wild P, Moulin JJ, Hammon B, Rosmorduc B, Rondeau du Noyer C, Lavandier M, Moline J. 1994. Lung cancer mortality in a French cohort of hard-metal workers. *Am J Ind Med* 26(5): 585-595.
- Lasfargues G, Lardot C, Delos M, Lauwerys R, Lison D. 1995. The delayed lung responses to single and repeated intratracheal administration of pure cobalt and hard metal powder in the rat. *Environ Res* 69(2): 108-121.
- Linnainmaa M, Kiilunen M. 1997. Urinary cobalt as a measure of exposure in the wet sharpening of hard metal and stellite blades. *Int Arch Occup Environ Health* 69(3): 193-200.
- Lison D. 1996. Human toxicity of cobalt-containing dust and experimental studies on the mechanism of interstitial lung disease (hard metal disease). *Crit Rev Toxicol* 26(6): 585-616.
- Lison D, Lauwerys R. 1992. Study of the mechanism responsible for the elective toxicity of tungsten carbide-cobalt powder toward macrophages. *Toxicol Lett* 60(2): 203-210.
- Lison D, Lauwerys R. 1993. Evaluation of the role of reactive oxygen species in the interactive toxicity of carbide-cobalt mixtures on macrophages in culture. *Arch Toxicol* 67(5): 347-351.
- Lison D, Lauwerys R. 1994. Cobalt bioavailability from hard metal particles: Further evidence that cobalt alone is not responsible for the toxicity of hard metal particles. *Arch Toxicol* 68(8): 528-531.
- Lison D, Buchet JP, Swennen B, Molders J, Lauwerys R. 1994. Biological monitoring of workers exposed to cobalt metal, salt, oxides, and hard metal dust. *Occup Environ Med* 51(7): 447-450.
- Lison D, Carboneille P, Mollo L, Lauwerys R, Fubini B. 1995. Physicochemical mechanism of the interaction between cobalt metal and carbide particles to generate toxic activated oxygen species. *Chem Res Toxicol* 8(4): 600-606.
- Lison D, Lauwerys R, Demedts M, Nemery B. 1996. Experimental research into the pathogenesis of cobalt/hard metal lung disease. *Eur Respir J* 9(5): 1024-1028.
- Lloyd DR, Carmichael PL, Phillips DH. 1998. Comparison of the formation of 8-hydroxy-2'-deoxyguanosine and single- and double-strand breaks in DNA mediated by Fenton reactions. *Chem Res Toxicol* 11(5): 420-427.
- Lombaert N, De Boeck M, Ecordier I, Undari E, Lison D, Irsch-Volders M. 2004. Evaluation of the apoptogenic potential of hard metal dust (WC-Co), tungsten carbide, and metallic cobalt. *Toxicol Lett* 154: 23-34.
- Lombaert N, Lison D, Van Hummelen P, Kirsch-Volders M. 2008. *In vitro* expression of hard metal dust (WC-Co)-responsive genes in human peripheral blood mononucleated cells. *Toxicol Appl Pharmacol* 227: 299-312.
- Mateuca R, Aka PV, De Boeck M, Hauspie R, Kirsch-Volders M, Lison D. 2005. Influence of *hOGG1*, *XRCC1* and *XRCC3* genotypes on biomarkers of genotoxicity in workers exposed to cobalt or hard metal dusts. *Toxicol Lett* 156(2): 277-288.
- McDermott FT. 1971. Dust in the cemented carbide industry. *Am Ind Hyg Assoc J* 32(3): 188-193.
- Moulin JJ, Wild P, Romazini S, Lasfargues G, Peltier A, Bozec C, Deguerre P, Pellet F, Perdrix A. 1998. Lung cancer risk in hard-metal workers. *Am J Epidemiol* 148(3): 241-248.
- Murata M, Gong P, Suzuki K, Koizumi S. 1999. Differential metal response and regulation of human heavy metal-inducible genes. *J Cell Physiol* 180(1): 105-113.
- Nackerdien Z, Kasprzak KS, Rao G, Halliwell B, Dizdaroğlu M. 1991. Nickel(II)- and cobalt(II)-dependent damage by hydrogen peroxide to the DNA bases in isolated human chromatin. *Cancer Res* 51(21): 5837-5842.
- Nicolaou G, Pietra R, Sabbioni E, Mosconi G, Cassina G, Seghizzi P. 1987. Multielement determination of metals in biological specimens of hard metal workers: a study carried out by neutron activation analysis. *J Trace Elem Electrolytes Health Dis* 1(2): 73-77.
- NTP. 2009. *Report on Carcinogens Background Document for Cobalt-Tungsten Carbide Powders and Hard Metals*. National Toxicology Program. http://ntp.niehs.nih.gov/ntp/roc/twelfth/2010/finalbds/hardmetalsbd20100408_508.pdf.
- Pellet F, Perdrix A, Vincent M, Mallion JM. 1984. Biological levels of urinary cobalt. *Arch Mal Prof* 45: 81-85 (as cited in Angerer and Heinrich 1988).
- Pulido MD, Parrish AR. 2003. Metal-induced apoptosis: mechanisms. *Mutat Res* 533(1-2): 227-241.
- Rizzato G, Lo Cicero S, Barberis M, Torre M, Pietra R, Sabbioni E. 1986. Trace of metal exposure in hard metal lung disease. *Chest* 90(1): 101-106.
- Sabbioni E, Minoia C, Pietra R, Mosconi G, Forni A, Scansetti G. 1994a. Metal determinations in biological specimens of diseased and non-diseased hard metal workers. *Sci Total Environ* 150(1-3): 41-54.
- Sabbioni E, Mosconi G, Minoia C, Seghizzi P. 1994b. The European Congress on cobalt and hard metal disease. Conclusions, highlights and need of future studies. *Sci Total Environ* 150(1-3): 263-270.
- Santhanam AT. 2003. Carbides, cemented. In *Kirk-Othmer Encyclopedia of Chemical Technology*, vol. 4. Online edition. New York: John Wiley & Sons. pp. 655-674.
- Scansetti G, Lamon S, Talarico S, Botta GC, Spinelli P, Sulotto F, Fantoni F. 1985. Urinary cobalt as a measure of exposure in the hard metal industry. *Int Arch Occup Environ Health* 57(1): 19-26.
- Scansetti G, Botta GC, Spinelli P, Reviglio L, Ponzetti C. 1994. Absorption and excretion of cobalt in the hard metal industry. *Sci Total Environ* 150(1-3): 141-144.
- Scansetti G, Maina G, Botta GC, Bambace P, Spinelli P. 1998. Exposure to cobalt and nickel in the hard-metal production industry. *Int Arch Occup Environ Health* 71(1): 60-63.
- Sheppard PR, Ridenour G, Speakman RJ, Witten ML. 2006. Elevated tungsten and cobalt in airborne particulates in Fallon, Nevada: possible implications for the childhood leukemia cluster. *Appl Geochem* 21: 152-165.
- Shi H, Hudson LG, Liu KJ. 2004. Oxidative stress and apoptosis in metal ion-induced carcinogenesis. *Free Radic Biol Med* 37(5): 582-593.
- Sprince NL, Chamberlin RI, Hales CA, Weber AL, Kazemi H. 1984. Respiratory disease in tungsten carbide production workers. *Chest* 86(4): 549-557.
- Stefaniak AB, Day GA, Harvey CJ, Leonard SS, Schwegler-Berry DE, Chipera SJ, Sahakian NM, Chisholm WP. 2007. Characteristics of dusts encountered during the production of cemented tungsten carbides. *Ind Health* 45:793-803.
- Stefaniak AB, Virji MA, Day GA. 2009. Characterization of exposures among cemented tungsten carbide workers. Part I: Size-fractionated exposures to airborne cobalt and tungsten particles. *J Expo Sci Environ Epidemiol* 19(5): 475-491.
- Stefaniak AB, Harvey CJ, Bukowski VC, Leonard SS. 2010. Comparison of free radical generation by pre- and post-sintered cemented carbide particles. *J Occup Environ Hyg* 7: 23-34.
- Stopford W, Turner J, Cappellini D, Brock T. 2003. Bioaccessibility testing of cobalt compounds. *J Environ Monit* 5(4): 675-680.
- Sueker JK. 2006. Comment on "Elevated tungsten and cobalt in airborne particulates in Fallon, Nevada: Possible implications for the childhood leukemia cluster," by Sheppard PR, Ridenour G, Speakman RJ, and Witten ML. *Appl Geochem* 21: 1083-1085.
- ThomasNet. 2008. *Metals: Carbide*. Thomas Publishing. <http://www.thomasnet.com/products/tungsten-carbide-89540207-1.html>. Last accessed: 9/24/08.
- Torra M, Fernández J, Rodamilans M, Navarro AM, Corbella J. 2005. Biological monitoring of cobalt exposure: results in a non-exposed population and on workers of a hard metal manufacture. *Trace Elem Electrolyt* 22(3): 174-177.
- Upadhyaya GS. 1998a. Classification and applications of cemented carbides. In *Cemented Tungsten Carbides. Production, Properties, and Testing*. Westwood, NJ: Noyes Publications. pp. 288-293.
- Upadhyaya GS. 1998b. Crystal structure and phase equilibria. In *Cemented Tungsten Carbides. Production, Properties, and Testing*. Westwood, NJ: Noyes Publications. pp. 7-54.
- USGS. 2008a. *Mineral Industry Surveys: Cobalt in October, November and December 2007*. Reston, VA: U.S. Geological Survey.
- USGS. 2008b. *Mineral Industry Surveys: Tungsten in January 2008*. Reston, VA: U.S. Geological Survey.
- USITC. 2008. *USITC Interactive Tariff and Trade DataWeb*. United States International Trade Commission. http://dataweb.usitc.gov/scripts/user_set.asp and search on HTS no. 284990. Last accessed: 9/24/08.
- Van Goethem F, Lison D, Kirsch-Volders M. 1997. Comparative evaluation of the in vitro micronucleus test and the alkaline single cell gel electrophoresis assay for the detection of DNA damaging agents: genotoxic effects of cobalt powder, tungsten carbide and cobalt-tungsten carbide. *Mutat Res* 392(1-2): 31-43.
- Wild P, Perdrix A, Romazini S, Moulin JJ, Pellet F. 2000. Lung cancer mortality in a site producing hard metals. *Occup Environ Med* 57(8): 568-573.
- WSDLI. 1995. *Hard-Metal Workers Face Risks from Cobalt, Cadmium*. WISHA Hazard Alert. State of Washington Department of Labor and Industries. <http://www.lni.wa.gov/Safety/Basics/HazAlerts/951a.asp>.
- Zanetti G, Fubini B. 1997. Surface interaction between metallic cobalt and tungsten carbide particles as a primary cause of hard metal lung disease. *J Mater Chem* 7(8): 1647-1654.
- Zou W, Yan M, Xu W, Huo H, Sun L, Zheng Z, Liu X. 2001. Cobalt chloride induces PC12 cells apoptosis through reactive oxygen species and accompanied by AP-1 activation. *J Neurosci Res* 64(6): 646-653.

Nickel Compounds and Metallic Nickel

Introduction

Nickel compounds and metallic nickel have many industrial and commercial applications, including use in stainless steel and other nickel alloys, catalysts, batteries, pigments, and ceramics. Nickel and Certain Nickel Compounds were listed in the *First Annual Report on Carcinogens* (1980) as *reasonably anticipated to be human carcinogens*. Nickel compounds as a class were first listed as *known to be human carcinogens* in the *Tenth Report on Carcinogens* (2002); this listing supersedes the listing of "certain nickel compounds" and applies to all members of the class. Metallic nickel was reevaluated in 2000 and remains listed as *reasonably anticipated to be a human carcinogen*. Nickel alloys were reviewed in 2000 but were not recommended for listing in the Report on Carcinogens (see Appendix C).

The profiles for nickel compounds and metallic nickel follow this introduction. The evidence for carcinogenicity from cancer studies in experimental animals and humans is discussed separately for nickel compounds and metallic nickel. However, most of the information on mechanisms of carcinogenesis, properties, use, production, exposure, and regulations is common to both nickel compounds and metallic nickel and therefore is combined into one section following the discussions of cancer studies.

Nickel Compounds

No separate CAS No. assigned for nickel compounds as a class

Known to be human carcinogens

First listed in the *Tenth Report on Carcinogens* (2002)

Carcinogenicity

Nickel compounds are *known to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in humans, including epidemiological and mechanistic studies. The combined results of epidemiological studies, mechanistic studies, and cancer studies in rodents support the concept that nickel compounds generate nickel ions in target cells at sites critical for carcinogenesis, thus allowing consideration and evaluation of these compounds as a single group.

Cancer Studies in Humans

Several epidemiological cohort studies of workers exposed to various nickel compounds showed an elevated risk of death from lung cancer and nasal cancer. Although the precise nickel compound responsible for the carcinogenic effects in humans is not always clear, studies indicate that nickel sulfate and the combinations of nickel sulfides and oxides encountered in the nickel-refining industry cause cancer in humans. The International Agency for Research on Cancer concluded that there was sufficient evidence of the carcinogenicity of nickel compounds encountered in the nickel-refining industry in humans (IARC 1990). In an additional study, nickel-refinery workers exposed primarily to soluble nickel compounds had a significant excess risk of lung cancer, and smoking and nickel exposure had a synergistic effect on cancer risk (Anderson *et al.* 1996). These workers also had an excess risk of nasal cancer.

Cancer Studies in Experimental Animals

In rats and in some studies with mice, inhalation or intratracheal instillation of nickel subsulfide or nickel oxide led to dose-related induction of benign and malignant lung tumors, including carcinoma (IARC 1990, NTP 1996a,b). Inhalation of nickel compounds also

caused tumors at tissue sites other than the lung; in particular, benign or malignant adrenal-gland tumors (pheochromocytoma) were observed in rats (NTP 1996a,b). Injection of rodents with various nickel compounds was repeatedly shown to cause dose-dependent increases in tumors in several species and at several different sites. Subcutaneous, intramuscular, intraperitoneal, subperiosteal, intrafemoral, intrapleural, intracerebral, intrarenal, intratesticular, and intraocular injections of nickel compounds all caused cancer (usually sarcoma) at the injection site. Injection of nickel also produced distant tumors of the liver in some strains of mice. IARC concluded that there was sufficient evidence of the carcinogenicity of several nickel compounds (monoxides, hydroxides, and crystalline sulfides) in experimental animals (IARC 1990).

Soluble nickel acetate is a complete transplacental carcinogen in rats. Brief exposure of pregnant rats to nickel acetate by intraperitoneal injection during pregnancy caused pituitary cancer in the offspring. Transplacental exposure to nickel acetate followed by exposure of the offspring to barbitol (a known tumor promoter) caused kidney tumors (renal cortical and pelvic tumors) (Diwan *et al.* 1992). In adult rats, injection of soluble nickel salts followed by barbitol exposure caused kidney cancer (renal cortical adenocarcinoma) that frequently metastasized to the lung, liver, and spleen (Kasprzak *et al.* 1990).

Metallic Nickel

CAS No. 7440-02-0

Reasonably anticipated to be a human carcinogen

First listed in the *First Annual Report on Carcinogens* (1980)

Also known as Ni

Carcinogenicity

Metallic nickel is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Metallic nickel caused tumors in two rodent species, at several different tissue sites, and by several different routes of exposure. In both rats and hamsters, metallic nickel powder caused tumors when administered by intratracheal instillation or by subcutaneous, intramuscular, or intraperitoneal injection. Intratracheal instillation of metallic nickel powder primarily caused adenocarcinoma, whereas injection most frequently caused sarcoma, demonstrating that metallic nickel can induce both epithelial and connective-tissue tumors (IARC 1973, 1976, 1990).

Cancer Studies in Humans

The available epidemiological studies of workers exposed to metallic nickel are limited by inadequate exposure information, low exposure levels, short follow-up periods, and small numbers of cases.

Nickel Compounds and Metallic Nickel

Studies on Mechanisms of Carcinogenesis

The available evidence suggests that metallic nickel has carcinogenic properties because it can slowly dissolve in the body and release ionic nickel, an active genotoxic and carcinogenic form of nickel. There is no evidence to suggest that the mechanisms by which nickel causes tumors in experimental animals would not also operate in humans.

Report on Carcinogens, Fourteenth Edition

Many studies in cultured rodent and human cells have shown that a variety of nickel compounds, including both soluble and insoluble forms of nickel, caused genetic damage, including DNA strand breaks, mutations, chromosomal damage, cell transformation, and disrupted DNA repair. Chromosomal aberrations have been observed in humans occupationally exposed to nickel. Nickel can bind ionically to cellular components, including DNA. The reduction-oxidation activity of the nickel ion may produce reactive oxygen species that attack DNA, and exposure to nickel ion *in vitro* or *in vivo* can result in production of 8-hydroxy-2'-deoxyguanosine in target tissues for cancer caused by nickel (IARC 1990, Kasprzak *et al.* 1990).

The carcinogenic potency of various nickel compounds varies widely, based on solubility properties and speciation. Studies indicate that soluble nickel salts can be complete carcinogens (Diwan *et al.* 1992) or initiators of carcinogenesis (Kasprzak *et al.* 1990) at tissue sites distant from the site of administration, which confirms that ionic nickel is the carcinogenic species. Differences in the potency of nickel compounds may relate to the specific properties of the compounds that affect the availability of ionic nickel at target sites. The listings of nickel compounds and metallic nickel are based on a large body of scientific evidence supporting the concept that nickel ion is carcinogenic. The hazard associated with a particular nickel compound is related largely to the compound's propensity to release ionic nickel in the body. The evidence suggests that the relatively insoluble metallic nickel is less likely to present a carcinogenic hazard than are the nickel compounds that tend to release proportionately more nickel ion. This view agrees with that expressed by IARC (1990), which based its evaluation of the carcinogenicity of nickel compounds as a group on the combined results of human epidemiological studies, cancer studies in experimental animals, and other data supporting the "underlying concept that nickel compounds can generate nickel ions at critical sites in their target cells." The IARC review noted that the carcinogenicity of nickel compounds depends not solely on their capacity to release ionic nickel, but also on factors that promote localization of high concentrations of nickel ions at critical tissue sites. This conclusion is consistent with evidence from studies in experimental animals indicating that nickel compounds of moderate solubility can, under certain exposure conditions, be more carcinogenic than more soluble compounds. Therefore, it is difficult to predict with any certainty the relative carcinogenic hazard posed by a particular nickel compound without a full understanding of its ability to release ionic nickel under specific exposure conditions.

Properties

Metallic nickel is a group 10 metallic element. It is a lustrous, silvery, hard ferromagnetic metal or a gray powder. It has a vapor pressure of 1 mm Hg at 1,810°C. Metallic nickel is insoluble in water and ammonia, slightly soluble in hydrochloric acid and sulfuric acid, and soluble in dilute nitric acid. It is resistant to attack by air and water at standard temperatures. However, powdered nickel is reactive in air and may ignite spontaneously (IARC 1990, ATSDR 1997, HSDB 2009).

Nickel oxides and hydroxides are practically insoluble in water and soluble in acids and ammonium hydroxide. Nickel monoxide (also known as nickel oxide) is a green to black powder that becomes yellow when heated. The temperature at which the crystal is formed determines the color of the crystal. It is soluble in acids and ammonium hydroxide. Nickel monoxide reacts with acids to form nickel salts and soaps, and mixtures of nickel monoxide and barium oxide react violently with iodine and hydrogen sulfide in air. Nickel hydroxide occurs either as green crystals or as a black powder. It does not burn, but it may produce toxic gases when heated to decomposition. It is available at 97% purity (IARC 1990, HSDB 2009).

Nickel sulfides are insoluble in water, and some occur in more than one form. Nickel subsulfide (α form) occurs as lustrous pale-yellowish or bronze crystals that are soluble in nitric acid. Nickel sulfide occurs in three forms (α , β , and amorphous) as dark-green to black crystals or powder. Nickel disulfide occurs as black crystals or powder and decomposes at temperatures above 400°C (IARC 1990).

Nickel salts are green to yellow crystals that generally are soluble in water and decompose when heated. Nickel acetate occurs as a dull-green powder that effloresces somewhat in air. It is available as the tetrahydrate at greater than 97% purity. Nickel chloride occurs as yellow (anhydrous) or green (hexahydrate) deliquescent crystals. It is soluble in ethanol and ammonium hydroxide and insoluble in ammonia. The hexahydrate form is available as a laboratory reagent at greater than 99% purity or as industrial products containing approximately 24.7% nickel. Nickel sulfate occurs as yellow, green, or blue crystals and is available in anhydrous, hexahydrate, or heptahydrate forms. The hexahydrate melts at 53.3°C and the heptahydrate at 99°C; both forms are available at greater than 99% purity. Nickel carbonate occurs as light-green rhombic crystals. It is practically insoluble in water but soluble in dilute acids and ammonia. Laboratory reagent grades contain 45% or 47.5% nickel, and industrial grades contain approximately 45% nickel (IARC 1990, HSDB 2009).

Nickel carbonyl occurs as a colorless, volatile, highly flammable liquid with a musty odor. It is practically insoluble in water but soluble in alcohol, benzene, chloroform, acetone, and carbon tetrachloride, and insoluble in dilute acids and dilute alkalis. It is available in a technical grade at greater than 99% purity. Nickel carbonyl decays spontaneously in air and may decompose violently when exposed to heat or flame in the presence of air or oxygen. When heated or on contact with acid or acid fumes, it emits toxic carbon monoxide fumes (HSDB 2009). Nickelocene occurs as dark-green crystals. It is insoluble in water but soluble in common organic solvents. It is highly reactive and decomposes in air, acetone, alcohol, and ether. It is available in solid form at greater than 90% purity or as an 8% to 10% solution in toluene (IARC 1990).

Physical and chemical properties of metallic nickel and selected nickel compounds are listed in the table on the next page, along with their chemical formulas.

Use

Because of its unique properties, nickel has many uses in industry. The majority (about 80%) of all nickel is used in alloys, because it imparts such properties as corrosion resistance, heat resistance, hardness, and strength (ATSDR 1997). The main uses of nickel are in the production of stainless steel, copper-nickel alloys, and other corrosion-resistant alloys. Pure nickel metal is used in electroplating, as a chemical catalyst, and in the manufacture of alkaline batteries, coins, welding products, magnets, electrical contacts and electrodes, spark plugs, machinery parts, and surgical and dental prostheses (IARC 1990, HSDB 2009). In 2009, 45% of the nickel used in the United States was used in stainless and alloy steel production, 39% in nonferrous alloys and superalloys, 11% in electroplating, and 5% in other uses. The end uses in 2009 were 32% in transportation, 14% in the chemical industry, 10% in electrical equipment, 8% in construction, 8% in fabricated metal products, 8% in the petroleum industry, 6% in household appliances, 6% in machinery, and 8% for other uses (Kuck 2010).

Nickel oxide sinters (a coarse form of nickel monoxide) are used in steel and alloy manufacturing. Green nickel monoxide is used in electronics, in fuel-cell electrodes, as a colorant in ceramics and glass, and to make nickel catalysts. Black nickel monoxide is used in the ceramics industry, to manufacture nickel catalysts, and to manufacture nickel salts. Nickel hydroxide is used in nickel-cadmium batter-

Substance	Formula	Atomic or molec. wt.	Specific gravity	Melting point	Boiling point
Metallic nickel	Ni	58.7	8.91	1,455°C	2,730°C
Nickel monoxide	NiO	74.7	6.72	1,955°C	NR
Nickel hydroxide	Ni(OH) ₂	92.7	4.1	230°C (dec)	N/A
Nickel acetate	Ni(C ₂ H ₃ O ₂) ₂	176.8	1.80	NR	16.6°C
Nickel chloride	NiCl ₂	129.6	3.51	1,001°C	973°C (sub)
Nickel sulfate	NiSO ₄	154.8	4.01	848°C (dec)	N/A
Nickel carbonate	NiCO ₃	118.7	4.39	dec	N/A
Nickel carbonyl	Ni(CO) ₄	170.7	1.32	-19°C	43°C

Source: HSDB 2009. NR = not reported; dec = decomposes; N/A = not applicable; sub = sublimes.

ies and as a catalyst intermediate. Nickel sulfides are used as catalysts in the petrochemical industry when high concentrations of sulfur are present in the distillates and as intermediates in hydrometallurgical processing of silicate-oxide nickel ores (IARC 1990). Nickel subsulfide is used in lithium batteries (HSDB 2009).

Nickel salts are widely used in industry. Nickel acetate is used as a catalyst intermediate, as a dye fixative in the textile industry, in electroplating, and as a sealer for anodized aluminum. Nickel chloride is used in nickel catalysts, to absorb ammonia in industrial gas masks, and in electroplating. Nickel sulfates are used in electroplating and electrodeless nickel plating, as chemical intermediates to produce other nickel compounds, and in nickel flashings on steel to prepare it to be porcelain-enameled. Nickel carbonate is used to prepare nickel monoxide, nickel powder, nickel catalysts, colored glass, and certain nickel pigments. It also is used in electroplating and as a catalyst to remove organic contaminants from water (IARC 1990, HSDB 2009).

Nickel carbonyl is used in the production of high-purity nickel powder by the Mond process and for continuous nickel coatings on steel and other metals. It also has many small-scale applications, such as vapor plating of nickel and deposition of nickel in semiconductor manufacturing. Nickelocene is used as a catalyst and complexing agent (IARC 1990).

Production

Nickel is refined from either sulfide or silicate-oxide ores, which generally contain no more than 3% nickel. Magmatic sulfide ores are mined underground or by open-pit methods. Pentlandite ([NiFe]S₈) is the principal sulfide ore; the largest known deposit is in Ontario, Canada, and substantial deposits are found in Minnesota, South Africa, Russia, Finland, and western Australia. Silicate-oxide ores, or garnierites, originate in (current or former) humid tropical regions and are surface mined by open-pit methods (IARC 1990, ATSDR 1997). Primary nickel production from mines in the United States was steady from the late 1950s to 1980, ranging from 10,000 to 14,000 metric tons (22 million to 31 million pounds) per year (USGS 2010). After 1980, primary production of nickel in the United States started declining, and no primary production has occurred since 1998, when 4,290 metric tons (9.5 million pounds) was produced.

Recycled scrap metal accounts for a large part of the nickel supply; in addition, relatively small quantities of nickel are recovered as a by-product at copper and precious-metal refineries or from reclamation of spent catalysts (Kuck 2009). Production from these secondary sources increased steadily from 21,000 metric tons (46 million pounds) in 1970 to a high of 106,000 metric tons (234 million pounds) in 2006, then declined to 63,500 metric tons (140 million pounds) in 2009.

From 1980 to 2008, U.S. consumption of nickel ranged from 163,000 to 250,000 metric tons (359 to 551 million pounds); consumption was highest in 2006 (USGS 2010). In 2009, consumption was 152,000 metric tons (335 million pounds), the lowest level since 1972 (Kuck 2010, USGS 2010). The demand for nickel is expected to

grow because of increased demand for nickel-based batteries and nickel-bearing superalloys used in aircraft engines (Kuck 2009), with the United States being dependent on foreign sources for most nickel supplies.

From 1980 to 2008, U.S. imports of nickel remained fairly steady, ranging from 117,000 to 190,000 metric tons (258 million to 419 million pounds); 149,000 metric tons (329 million pounds) was imported in 2008. In 2009, imports fell to 114,800 metric tons (253 million pounds). U.S. exports of nickel ranged from 17,700 to 67,300 metric tons (39 to 148 million pounds) between 1980 and 2006, increasing to 116,000 metric tons (256 million pounds) in 2007, and were 99,680 metric tons (220 million pounds) in 2009 (Kuck 2010, USGS 2010).

Exposure

Environmental exposure to nickel occurs through inhalation, ingestion, and dermal contact. The general population is exposed to low levels of nickel because it is widely present in air, water, food, and consumer products. The general population takes in most nickel through food; the average daily intake from food in the United States is estimated at 150 to 168 µg. Typical daily intake from drinking water is 2 µg and from air is 0.1 to 1 µg. The general population is also exposed to nickel in nickel alloys and nickel-plated materials, such as coins, steel, and jewelry, and residual nickel may be found in soaps, fats, and oils (ATSDR 1997).

According to the U.S. Environmental Protection Agency's Toxics Release Inventory, releases of nickel to the environment trended downwards from 1988 to 2003 and then increased, while releases of nickel compounds increased until 1998 but have since decreased by half. In 2007, 1,552 facilities released 8.3 million pounds of nickel, and 1,027 facilities released 30.5 million pounds of nickel compounds (TRI 2009).

Occupational exposure to nickel occurs mainly through inhalation of dust particles and fumes or through dermal contact. Nickel workers can also ingest nickel-containing dusts. Occupational exposure is common for workers involved in mining, smelting, welding, casting, spray-painting and grinding, electroplating, production and use of nickel catalysts, polishing of nickel-containing alloys, and other jobs where nickel and nickel compounds are produced or used (HSDB 2009). The National Occupational Hazard Survey (conducted from 1972 to 1974) estimated that 23,272 workers potentially were exposed to nickel and nickel compounds (NIOSH 1976), and the National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 507,681 workers, including 19,673 women, potentially were exposed to nickel (molecular formula unknown) (NIOSH 1990).

Regulations

Department of Transportation (DOT)

Nickel carbonyl, nickel cyanide, nickel nitrate, and nickel nitrite are considered hazardous materials, and special requirements have been set for marking, labeling, and transporting these materials; nickel picrate is forbidden from transport.

Report on Carcinogens, Fourteenth Edition

Nickel carbonyl, nickel cyanide, and nickel tetracarbonyl are considered marine pollutants and special requirements have been set for marking, labeling, and transporting these materials.

Environmental Protection Agency (EPA)

Clean Air Act

Mobile Source Air Toxics: Nickel compounds are listed as mobile-source air toxics for which regulations are to be developed.

National Emission Standards for Hazardous Air Pollutants: Nickel and its compounds are listed as hazardous air pollutants.

Prevention of Accidental Release: Threshold quantity (TQ) = 1,000 lb for nickel carbonyl.

Urban Air Toxics Strategy: Nickel compounds are identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Clean Water Act

Biosolids Rule: Limits have been established for nickel in biosolids (sewage sludge) when used or disposed of via land application, surface disposal, or incineration.

Effluent Guidelines: Nickel and nickel compounds are listed as toxic pollutants.

Water Quality Criteria: Based on fish or shellfish and water consumption = 610 µg/L for metallic nickel; based on fish or shellfish consumption only = 4,600 µg/L for metallic nickel.

Numerous nickel compounds are designated as hazardous substances.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 100 lb for nickel, nickel ammonium sulfate, nickel chloride, nickel nitrate, and nickel sulfate; 10 lb for nickel carbonyl, nickel cyanide, and nickel hydroxide.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Nickel and nickel compounds are listed substances subject to reporting requirements.

Threshold planning quantity (TPQ) = 1 lb for nickel carbonyl.

Reportable quantity (RQ) = 10 lb for nickel carbonyl.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of nickel or nickel compounds = P073, P074, F006.

Nickel and nickel compounds are listed as hazardous constituents of waste.

Food and Drug Administration (FDA)

Maximum permissible level of nickel in bottled water = 0.1 mg/L.

The color additives ferric ammonium ferrocyanide and ferric ferrocyanide, when used in drugs, may contain nickel at levels no greater than 200 ppm.

Menhaden oil may contain nickel at concentrations not to exceed 0.5 ppm.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.

Permissible exposure limit (PEL) = 1 mg/m³ for elemental nickel and compounds other than nickel carbonyl; = 0.001 ppm (0.007 mg/m³) for nickel carbonyl.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value - time-weighted average (TLV-TWA) = 1.5 mg/m³ for elemental nickel; = 0.1 mg/m³ for soluble inorganic nickel compounds and nickel subsulfide; = 0.2 mg/m³ for insoluble inorganic nickel compounds.

Threshold limit value - ceiling (TLV-C) = 0.05 ppm for nickel carbonyl.

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (REL) = 0.015 mg/m³ for elemental nickel and nickel compounds other than nickel carbonyl; = 0.001 ppm (0.007 mg/m³) for nickel carbonyl.

Immediately dangerous to life and health (IDLH) limit = 10 mg/m³ for elemental nickel and nickel compounds other than nickel carbonyl; = 2 ppm (14 mg/m³) for nickel carbonyl.

Metallic nickel and nickel compounds are listed as potential occupational carcinogens.

References

- Andersen A, Berge SR, Engeland A, Norseth T. 1996. Exposure to nickel compounds and smoking in relation to incidence of lung and nasal cancer among nickel refinery workers. *Occup Environ Med* 53(10): 708-713.
- ATSDR. 1997. *Toxicological Profile for Nickel*. Agency for Toxic Substances and Disease Registry. <http://www.atsdr.cdc.gov/toxprofiles/tp15.pdf>. 293 pp.
- Diwan BA, Kasprzak KS, Rice JM. 1992. Transplacental carcinogenic effects of nickel(II) acetate in the renal cortex, renal pelvis and adenohypophysis in F344/NCr rats. *Carcinogenesis* 13(8): 1351-1357.
- HSDB. 2009. *Hazardous Substances Data Bank*. National Library of Medicine. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB> and search on CAS number. Last accessed: 10/22/09
- IARC. 1973. Nickel and inorganic nickel compounds. In: *Some Inorganic and Organometallic Compounds. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans*, vol. 2. Lyon, France: International Agency for Research on Cancer. pp. 126-149.
- IARC. 1976. Nickel and nickel compounds. In: *Cadmium, Nickel, Some Epoxides, Miscellaneous Industrial Chemicals and General Considerations on Volatile Anaesthetics. IARC Monographs on the Evaluation of*

Carcinogenic Risk of Chemicals to Humans, vol. 11. Lyon, France: International Agency for Research on Cancer. pp. 75-112.

IARC. 1990. Nickel and nickel compounds. In *Chromium, Nickel and Welding. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans*, vol. 49. Lyon, France: International Agency for Research on Cancer. pp. 257-445.

Kasprzak KS, Diwan BA, Konishi N, Misra M, Rice JM. 1990. Initiation by nickel acetate and promotion by sodium barbital of renal cortical epithelial tumors in male F344 rats. *Carcinogenesis* 11(4): 647-652.

Kuck PH. 2009. *2007 Minerals Yearbook: Nickel [Advance Release]*. U.S. Geological Survey. <http://minerals.usgs.gov/minerals/pubs/commodity/nickel/myb1-2007-nicke.pdf>.

Kuck, PH. 2010. Nickel. In *Mineral Commodity Summaries*. U.S. Geological Survey. <http://minerals.usgs.gov/minerals/pubs/commodity/nickel/mcs-2010-nicke.pdf>.

NIOSH. 1976. *National Occupational Hazard Survey (1972-74)*. DHEW (NIOSH) Publication No. 78-114. Cincinnati, OH: National Institute for Occupational Safety and Health.

NIOSH. 1990. *National Occupational Exposure Survey (1981-83)*. National Institute for Occupational Safety and Health. Last updated: 7/1/90. <http://www.cdc.gov/noes/noes1/50420sic.html>.

NTP. 1996a. *Toxicology and Carcinogenesis Studies of Nickel Oxide (CAS No. 1313-99-1) in F344 Rats and B6C3F₁ Mice (Inhalation Studies)*. Technical Report Series no. 451. Research Triangle Park, NC: National Toxicology Program. 381 pp.

NTP. 1996b. *Toxicology and Carcinogenesis Studies of Nickel Subsulfide (CAS No. 12035-72-2) in F344 Rats and B6C3F₁ Mice (Inhalation Studies)*. Technical Report Series no. 453. Research Triangle Park, NC: National Toxicology Program. 365 pp.

TRI. 2009. *TRI Explorer Chemical Report*. U.S. Environmental Protection Agency. Last updated: 5/14/08. <http://www.epa.gov/triexplorer> and select Nickel.

USGS. 2010. Nickel statistics. In *Historical Statistics for Mineral and Material Commodities in the United States*. Last updated 1/8/10. U.S. Geological Survey. <http://minerals.usgs.gov/ds/2005/140/nickel.pdf>.

Exhibit 26

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Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures

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LIST OF ABBREVIATIONS

ACGIH	American Conference of Government Industrial Hygienists
AHH	Aryl Hydrocarbon Hydroxylase
ATSDR	Agency for Toxic Substances and Disease Registry
B[a]P	Benzo(a)pyrene
BINWOE	Binary Weight-of-Evidence
BMD	Benchmark Dose
CRAVE	Carcinogen Risk Assessment Verification Endeavor
ED _x	Effective Dose in x Percent of Test Animals
GSH	Glutathione
HI	Hazard Index
HQ	Hazard Quotient
IRIS	Integrated Risk Information System
LD _x	Lethal Dose in x Percent of Test Animals
LOAEL	Lowest-Observed-Adverse-Effect Level
MFO	Mixed Function Oxidase
MOAEL	Minimum-Observed-Adverse-Effect Level
MOE	Margins of Exposure
MT	Metallothionein
NAS	National Academy of Sciences
NOAEL	No-Observed-Adverse-Effect Level
NRC	National Research Council

LIST OF ABBREVIATIONS (continued)

OSHA	Occupational Safety and Health Administration
PAH	Polycyclic Aromatic Hydrocarbon
PBPK	Physiologically Based Pharmacokinetics
PBPK/PD	Physiologically Based Pharmacokinetics and Pharmacodynamics
PCB	Polychlorinated Biphenyl
POM	Polycyclic Organic Material
RfC	Reference Concentration
RfD	Reference Dose
RPF	Relative Potency Factor
TEF	Toxicity Equivalence Factor
TEQ	2,3,7,8-TCDD Toxicity Equivalents
TOC	Total Organic Carbon
TTC	Toxicity-Specific Concentration
TTD	Target Organ Toxicity Dose
UF	Uncertainty Factor
WHO	World Health Organization
WOE	Weight of Evidence

PREFACE

The U.S. EPA's Risk Assessment Forum (Forum) is publishing the *Supplemental Guidance for Conducting Health Risk Assessment of Chemical Mixtures* as a supplement to the EPA's *Guidelines for the Health Risk Assessment of Chemical Mixtures (Guidelines)* (U.S. EPA, 1986) (Appendix A). The 1986 Guidelines represent the Agency's science policy and are a procedural guide for evaluating data on the health effects from exposures to chemical mixtures. The principles and concepts put forth in the Guidelines remain in effect. However, where the Guidelines describe broad principles and include few specific procedures, the present guidance is a supplement that is intended to provide more detail on these principles and procedures.

To address concerns over health risks from multichemical exposures, the U.S. Environmental Protection Agency published the *Guidelines for the Health Risk Assessment of Chemical Mixtures* in 1986 (U.S. EPA, 1986) (Appendix A). The Guidelines describe broad concepts related to mixture exposure and toxicity and include few specific procedures. In 1989 EPA published guidance for the Superfund program on hazardous waste that gave practical steps for conducting a mixtures risk assessment (U.S. EPA, 1989a). Also in 1989, EPA published the revised document on the use of Toxicity Equivalence Factors for characterizing health risks of the class of chemicals including the dibenzo-dioxins and dibenzofurans (U.S. EPA, 1989b). In 1990, EPA published a Technical Support Document to provide more detailed information on toxicity of whole mixtures and on toxicologic interactions (e.g., synergism) between chemicals in a binary (two-chemical) mixture (U.S. EPA, 1990). The concept of toxicologic similarity was also discussed. The Environmental Criteria and Assessment Office (now the National Center for Environmental Assessment) followed this with the production of a *Technical Support Document on Health Risk Assessment of Chemical Mixtures* (U.S. EPA, 1990b).

This supplementary guidance document is a result of several influences. Because the science of environmental risk assessment has continued to evolve and EPA has learned from an array of experiences, the Agency charged the Risk Assessment Forum with developing guidance on challenging issues such as cumulative risk assessment. Part of the Forum's response to this charge was to establish a Technical Panel to ensure that the advances in the area of chemical mixtures health risk assessment are reflected in Agency-wide guidance materials. Through the evaluation of waste sites for mixtures risks it has become apparent that the exposure scenarios for these sites are extremely diverse. Moreover, the quality and quantity of pertinent information available for risk assessment has varied considerably for different mixtures. Other Agency and external initiatives have influenced the development of the chemical mixtures supplementary guidance:

- The National Academy of Sciences has issued a recommendation to move away from single-chemical assessments. (NRC, 1994)
- In 1997, EPA's Science Policy Council issued a policy statement on cumulative risk assessment. This policy addressed the first step in the overall assessment process (i.e., problem formulation) (U.S. EPA, 1997a).
- Siting activities have raised the issue of multiple chemical exposures. Parties are concerned not only about what risks are associated with releases from a particular facility, but also the potential combined effects of exposures from other sources in the area.
- EPA's research strategy for 2000 and beyond emphasizes research on chemical mixtures.

When the 1986 Guidelines were published, the Agency recognized that the Guidelines would need to be updated as the science of chemical mixture assessment evolved. Research efforts were undertaken immediately and by 1988 Agency offices were discussing revision topics. By 1989, under the auspices of the Risk Assessment Forum, efforts were underway to revise the Guidelines. Updates to the Guidelines were reviewed in a June 1997 *Internal Risk Assessment Forum Review Draft of the Guidance on Health Risk Assessment of Chemical Mixtures*. The Technical Panel revised the document in accordance with comments received during the July 1997 review. In June 1998 the Forum sponsored an Agency review and colloquium. Over the next months the Technical Panel worked with commenters to address issues raised during the 1998 colloquium to prepare the document for external peer review. It was determined at this time that the broad principles and concepts put forth in the 1986 Guidelines remained applicable, but needed more detail. As a result it was determined that the document would supplement, and not replace the 1986 Guidelines. An external peer review was convened in May 1999. Twelve independent experts representing consulting, academia, industry, the U.S. Department of Health Agency for Toxic Substances and Disease Registry, and the TNO Nutritional and Food Research Institute of the Netherlands, reviewed the revised supplementary document dated April 1999. The experts provide comments that reflected their experience and expertise in toxicology, mechanistic and pharmacokinetic modeling, statistics, and risk assessment (risk assessment of chemical classes, of complex and unidentifiable mixtures, and of multi-chemical exposures at Superfund sites). Their comments are documented in the report entitled, *Report of the Peer Review Workshop on the Guidance for Conducting Health Risk*

Assessments of Chemical Mixtures (Eastern Research Group Inc., 1999). During the summer of 1999 the Technical Panel considered comments from the external experts and from the Forum in revising and reorganizing the supplementary document. This series of internal and external reviews has ensured that the supplementary guidance is consistent with related science and Agency guidance developments.

After an abbreviated overview of the background and scope, the *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures* document puts forth the risk assessment paradigm for mixtures. This paradigm begins with problem formulation, then briefly discusses hazard identification, dose-response assessment, exposure, and risk characterization. The document is organized according to the type of data available to the risk assessor, ranging from data-rich to data-poor situations. (See Figure 2-1). Procedures are described for assessment using data on the mixture of concern, data on a toxicologically similar mixture, and data on the mixture component chemicals. The state of the science varies dramatically for these three approaches. The whole-mixture procedures are most advanced for assessing carcinogenic risk, mainly because of the long use of in vitro mutagenicity tests to indicate carcinogenic potency. In vitro test procedures for noncancer endpoints are still in the pioneering stage. In contrast, the component-based procedures, particularly those that incorporate information on toxicologic interactions, are most advanced for noncarcinogenic toxicity. No single approach is recommended in this supplementary guidance. Instead, guidance is given for the use of several approaches depending on the nature and quality of the data. The appendices contain definitions, a discussion on toxicologic interactions and pharmacokinetic models, and a reprint of the 1986 Guidelines.

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EXECUTIVE SUMMARY

This supplementary guidance document is organized according to the type of data available to the risk assessor, ranging from data rich to data poor situations. This organization reflects the approaches to chemical mixture risk assessment recommended in the 1986 *Guidelines for the Health Risk Assessment of Chemical Mixtures* (Appendix A). This document describes more detailed procedures for chemical mixture assessment using data on the mixture of concern, data on a toxicologically similar mixture, and data on the mixture component chemicals. The state-of-the-science varies dramatically for these three approaches. It is recommended that the risk assessor implement several of the approaches that are practical to apply and evaluate the range of health risk estimates that are produced.

This document suggests that the selection of a chemical mixture risk assessment method follows the outline in the flow chart shown in Figure 2-1, which begins with an assessment of data quality and then leads the risk assessor to selection of a method through evaluation of the available data. The major concerns for the user are whether the available data are on components or whole mixtures, whether the data are composed of either similar components or similar mixtures that can be thought of as acting by similar toxicologic processes, and whether the data may be grouped by emissions source, chemical structure, or biologic activity. Method-specific user fact sheets for quantitative risk assessment can be found in Sections 2.5 and 2.6 and are intended to provide a concise overview of each currently available method. These fact sheets provide the following information relative to the risk assessment approach:

- Type of Assessment
- Data Requirements
- Section(s)
- References
- Strategy of Method
- Ease of Use
- Assumptions
- Limitations
- Uncertainties

In Figure 2-1, an evaluation of the data may lead the user to decide that only a qualitative analysis should be performed. This generally occurs in cases where data quality is poor, inadequate quantitative data are available, data on a similar mixture cannot be classified as

“sufficiently similar” to the mixture of concern, exposures cannot be characterized with confidence, or method-specific assumptions about the toxicologic action of the mixture or of its components cannot be met. When this occurs, the risk assessor can still perform a qualitative assessment that characterizes the potential human health impacts from exposure to that mixture. Such a risk characterization should discuss each element of the risk assessment paradigm, including available information on the mixture itself, on its components, and on potential interactions among the components. Any information on fate and transport of the mixture that would affect its final composition at the time of exposure should be noted.

The assessment of chemical mixtures is an area of active scientific investigation. As new information relevant to health risk from exposure to chemical mixtures becomes available, additional guidance documents will be published.

1. INTRODUCTION

1.1. BACKGROUND

Although some potential environmental hazards involve significant exposure to only a single compound, most instances of environmental contamination involve concurrent or sequential exposures to a mixture of compounds that may induce similar or dissimilar effects over exposure periods ranging from short-term to lifetime. For the purposes of this guidance document, a mixture will be defined as any combination of two or more chemical substances, regardless of source or of spatial or temporal proximity, that can influence the risk of chemical toxicity in the target population (U.S. EPA, 1986). In some instances, the mixtures are highly complex, consisting of scores of compounds that are generated simultaneously as by-products from a single source or process (e.g., coke oven emissions and diesel exhaust). In other cases, complex mixtures of related compounds are produced as commercial products (e.g., PCBs, gasoline and pesticide formulations) and eventually released into the environment. Another category of mixtures consists of compounds, often unrelated chemically or commercially, that are placed in the same area for disposal or storage, and have the potential for combined exposure to humans. Multichemical exposures are ubiquitous, including air and soil pollution from municipal incinerators, leakage from hazardous waste facilities and uncontrolled waste sites, and drinking water containing chemical substances formed during disinfection.

To address concerns over health risks from multichemical exposures, the U.S. Environmental Protection Agency, hereafter referred to as EPA, issued *Guidelines for the Health Risk Assessment of Chemical Mixtures* in 1986 (U.S. EPA, 1986) (Appendix A). Those Guidelines described broad concepts related to mixture exposure and toxicity and included few specific procedures. In 1989, EPA published guidance for the Superfund program on hazardous waste that gave practical steps for conducting a mixtures risk assessment (U.S. EPA, 1989a). Also in 1989, EPA published the revised document on the use of Toxicity Equivalence Factors for characterizing health risks of the class of chemicals including the dibenzo-dioxins and dibenzofurans (U.S. EPA, 1989b). In 1990, EPA published a Technical Support Document to provide more detailed information on toxicity of whole mixtures and on toxicologic interactions (e.g., synergism) between chemicals in a binary (two-chemical) mixture (U.S. EPA, 1990). The concept of toxicologic similarity was also discussed.

As more waste sites were evaluated for mixtures risks, it became apparent that the exposure scenarios for these sites were extremely diverse. Moreover, the quality and quantity of pertinent information available for risk assessment varied considerably for different mixtures. Such difficulties continue. Occasionally, the chemical composition of a mixture is well characterized, levels of exposure to the population are known, and detailed toxicologic data on

the mixture are available. Most frequently, some components of the mixture are unknown, exposure data are uncertain or vary over time, and toxicologic data on the known components of the mixture are limited. Consequently, this document has been developed to supplement the earlier guidance documents and is organized according to the type of data available to the risk assessor, ranging from data-rich to data-poor situations. Procedures are described for assessment using data on the mixture of concern, data on a toxicologically similar mixture, and data on the mixture component chemicals. The state of science varies dramatically for these three approaches. The whole-mixture procedures are most advanced for assessing carcinogenic risk, mainly because of the long use of in vitro mutagenicity tests to indicate carcinogenic potency. In vitro test procedures for noncancer endpoints are still in the pioneering stage. In contrast, the component-based procedures, particularly those that incorporate information on toxicologic interactions, are most advanced for noncarcinogenic toxicity.

Mixture risk assessments usually involve substantial uncertainties. If the mixture is treated as a single complex substance, these uncertainties range from inexact descriptions of exposure to inadequate toxicity information. When viewed as a simple collection of a few component chemicals, the uncertainties include the generally poor understanding of the magnitude and nature of toxicologic interactions, especially those interactions involving three or more chemicals. Because of these uncertainties, the assessment of health risk from chemical mixtures should include a thorough discussion of all assumptions and the identification, when possible, of the major sources of uncertainty. No single approach is recommended in this supplementary guidance. Instead, guidance is given for the use of several approaches depending on the nature and quality of the data.

1.2. OVERVIEW

The primary purpose of this document is to generate a consistent Agency approach for assessing health risks from exposures to multiple chemicals, denoted in this guidance by the general term “mixtures.” The resulting mixtures risk assessments are intended to assist decision makers by characterizing health risks for the particular exposure conditions of interest. Because exposure scenarios and the available supporting data are highly diverse, this document has been developed as a procedural guide that emphasizes broad underlying principles of the various science disciplines (environmental chemistry, toxicology, pharmacology, statistics) necessary for providing information on the relationship between multichemical exposure and potential health effects. Specific approaches to be used for the evaluation of the various kinds of mixture data are also discussed.

This document addresses only risks to human health from multichemical exposures. Ecological effects are beyond its scope, even though many of the procedures might be adaptable

to ecological risk assessment from multiple stressors. Because other Agency guidelines exist that address exposure assessment and specific toxic endpoint evaluations, this guidance focuses on procedures for dose-response assessment and risk characterization.

It is not the intent of this guidance document to regulate any social or economic aspects concerning risk of injury to human health or the environment caused by exposure to a chemical agent(s). All such action is addressed in specific statutes and federal legislation and is independent of this guidance.

This guidance document represents a supplement to the original Guidelines of 1986 and is intended to reflect the evolutionary scientific development in the area of chemical mixtures risk assessment. New guidance has been provided that gives more specific details on the nature of the desired information and the procedures to use in analyzing the data. Among these are methods for using whole-mixture data on a toxicologically similar mixture, methods for incorporating information on toxicologic interactions to modify a Hazard Index (HI), and generalized procedures for mixtures involving classes of similar chemicals. There are also expanded discussions of the concerns when using only whole-mixture data as well as when using only data on the individual chemical components.

The assessment of chemical mixtures is an area of active scientific investigation. Some of the procedures herein for chemical mixtures have had little or no application to date in actual health risk assessments. Their use is encouraged, along with research on new procedures to improve or replace those discussed here. As new information relevant to health risk from exposure to chemical mixtures becomes available, additional guidance documents will be published.

2. APPROACH TO RISK ASSESSMENT OF CHEMICAL MIXTURES

2.1. THE RISK ASSESSMENT PARADIGM FOR MIXTURES

Human health risk assessments done by EPA generally follow the paradigm established by the National Academy of Sciences (NRC, 1983). This paradigm describes a group of interconnected processes for performing a risk assessment that include hazard identification, dose-response assessment, exposure assessment, and risk characterization. These four parts of the paradigm are used as the foundation for the procedures presented in this guidance. Preamble to all is problem formulation, which is defined in EPA's (1998a) Ecological Risk Assessment Guidelines as "a process for generating and evaluating preliminary hypotheses about why...effects have occurred or may occur." This EPA guidance for assessing risks from exposures to chemical mixtures begins with problem formulation as the initial step; much of the information about this key step has been adapted from the Ecological Risk Assessment Guidelines, and the reader is referred to Chapter 3 of that document for a more comprehensive discussion (U.S. EPA, 1998a).

2.1.1. Problem Formulation

Problem formulation, which provides the foundation for the entire risk assessment, consists of three initial steps: (1) evaluate the nature of the problem, (2) define the objectives of the risk assessment, and (3) develop a data analysis and risk characterization plan. The quality, quantity, and pertinence of information will determine the course of problem formulation. It concludes with three products: (1) selection of assessment endpoints, (2) review of the conceptual models that describe the relationship between exposure to a mixture of chemicals and risk, and (3) adjusting the analytic plan. (The pertinence of the information that is available at the outset of the assessment, in combination with the assessment objectives, will identify the types of information that should be collected through the analytic plan.) Ideally, the problem is formulated jointly by risk analysts and risk managers. While the steps and outcomes associated with problem formulation are presented separately, experiences from ecological applications and Superfund site assessments show the process to be frequently interactive and iterative rather than linear.

2.1.2. Hazard Identification and Dose-Response Assessment

In *hazard identification*, available data on biological endpoints are used to determine if a material is likely to pose a hazard to human health. These data are also used to define the type of potential hazard (e.g., does the material induce tumor formation or act as a kidney toxicant). In the *dose-response assessment*, data (most often from animal studies and occasionally from

human studies) are used to estimate the amount of material that may produce a given effect in humans. The risk assessor may calculate a quantitative dose-response relationship usable for low-dose exposure, often by applying mathematical models to the data.

2.1.3. Exposure

The *exposure assessment* seeks to determine the extent to which a population is exposed to the material. Exposure assessment uses available data relevant to population exposure, such as emissions data, measurement of the material in environmental media, and biomarker information. Fate and transport of the material in the environment, as well as media, pathways, and routes of exposure, may all be considered in the exposure assessment. Data limitations on the environmental concentrations of interest often necessitate the use of modeling to provide relevant estimates of exposure.

2.1.4. Risk Characterization and Uncertainty

Risk characterization is the integrating step in the risk assessment process that summarizes assessments of effects on human health and ecosystems and assessments of exposure from multiple environmental media, identifies human subpopulations or ecological species at elevated risk, combines these assessments into characterizations of human and ecological risk, and describes the uncertainty and variability in these characterizations. In March 1995, the Administrator of EPA issued the *Policy for Risk Characterization at the U.S. Environmental Protection Agency* (U.S. EPA, 1995). The purpose of this policy statement was to ensure that critical information from each stage of a risk assessment be presented in a manner that provides for greater clarity, transparency, reasonableness, and consistency in risk assessments. Most of the 1995 *Policy for Risk Characterization at the U.S. EPA* was directed toward assessment of human health consequences of exposures to an agent. Key aspects of risk characterization identified in the 1995 *Policy for Risk Characterization at the U.S. EPA* include these: bridging risk assessment and risk management, discussing confidence and uncertainties, and presenting several types of risk information. Another publication, *Science and Judgment in Risk Assessment* (NRC, 1994), produced primarily for implementation of the 1990 Amendment to the Clean Air Act but applicable more generally, emphasized that the goal of risk characterization is to provide understanding of the type and magnitude of potential adverse effects of an agent under the particular circumstances of its release.

2.1.5. Incorporating the Paradigm Into Mixtures Guidance

EPA regularly publishes guidelines to provide for consistency of application and communication of risk assessment. Guidelines were published in 1986 on assessment of the

following areas: exposure, developmental effects, germ cell mutagenicity, carcinogenic effects, and chemical mixtures (U.S. EPA, 1986, 1987). Since that time, the Agency has revised some of these Guidelines and also published new Guidelines. These include Guidelines on developmental toxicity (U.S. EPA, 1991a), exposure assessment (U.S. EPA, 1992), cancer (proposed revisions) (U.S. EPA, 1996a), reproductive toxicity (U.S. EPA, 1996c), and neurotoxicity (U.S. EPA, 1998b). All of the EPA guidelines for human health risk assessment incorporate the four parts of the NAS paradigm.

For this supplemental guidance on the risk assessment of chemical mixtures, the four parts of the paradigm are interrelated and will be found within the assessment techniques that are presented. For some methods described herein, assessment of dose-response relies both on decisions in the area of hazard identification and on assessment of potential human exposures. For mixtures, the use of pharmacokinetics data and models in particular differs from single-chemical assessment, where they are often part of the exposure assessment. For mixtures, the dominant mode of toxicologic interaction is the alteration of pharmacokinetic processes, which strongly depends on the exposure levels of the mixture chemicals. In this guidance, there has been no effort to categorize methods strictly or arbitrarily into one part of the paradigm. The methods are organized instead according to the type of available data. In general, risk characterization takes into account both human health and ecological effects, and also assesses multiroute exposures from multiple environmental media. This guidance focuses only on the human health risk assessment for chemical mixtures and only discusses multiroute exposures in terms of conversions from dermal to oral.

2.2. PROCEDURE FOR SELECTING A RISK ASSESSMENT METHOD

2.2.1. Introduction

The 1986 *Guidelines for the Health Risk Assessment of Chemical Mixtures* (U.S. EPA, 1986) (Appendix A) recommend three approaches to quantitative health risk assessment of a chemical mixture, depending upon the type of available data. In the first approach, toxicity data on the mixture of concern are available; the quantitative risk assessment is done directly from these preferred data. In the second approach, when toxicity data are not available for the mixture of concern, the Guidelines recommend using toxicity data on a “sufficiently similar” mixture. If the mixture of concern and the proposed surrogate mixture are judged to be similar, then the quantitative risk assessment for the mixture of concern may be derived from health effects data on the similar mixture. Finally, the third approach is to evaluate the mixture through an analysis of its components, e.g., using dose addition for similarly acting chemicals and response addition for independently acting chemicals. These procedures include a general assumption that interaction effects at low dose levels either do not occur at all or are small enough to be

insignificant to the risk estimate. The Guidelines recommend the incorporation of interactions data when available, if not as part of the quantitative process, then as a qualitative evaluation of the risk.

No single approach is recommended in this guidance document. Instead, guidance is given for the use of several approaches depending on the nature and quality of the available data, the type of mixture, the type of assessment being made, the known toxic effects of the mixture or of its components, the toxicologic or structural similarity of mixtures or of mixture components, and the nature of the environmental exposure. The approaches presented herein represent a mix of well-known, routine methods with several newer, less well-established techniques. As a collection, they provide the risk assessor with a number of reasonable options for evaluating risk for chemical mixtures.

2.2.2. Steps for Selection

This guidance suggests that the selection of a chemical mixture risk assessment method follow the outline in the flow chart shown in Figure 2-1, which begins with an assessment of data quality and then leads the risk assessor to selection of a method through evaluation of the available data. The major concerns for the user are whether the available data are on components or whole mixtures, whether the data are composed of either similar components or similar mixtures that can be thought of as acting by similar toxicologic processes, whether the mixture components act by the same mode of action or are functionally independent, or whether the data may be grouped by emissions source, chemical structure, or biologic activity.

This document is organized around the decision points in Figure 2-1, so that the user can refer to specific sections and find guidance on the issues to consider when working through the flow chart. Appendix B also offers the user a number of definitions to help clarify the terminology that is unique to chemical mixtures risk assessment. Table B-1 presents chemical mixture definitions in terms of specific criteria including the complexity of the mixture, similarity of biologic activity, similarity of chemical structure or mixture composition, the environmental source of the mixture, toxic endpoint, etc. Table B-2 provides definitions for terms that are used to describe various types of toxicologic interactions including forms of additivity, antagonism, synergism, and other toxicologic phenomena.

Method-specific user fact-sheets in Sections 2.5 and 2.6 are intended to provide a concise overview of each currently available method. These fact-sheets provide the following information relative to the risk assessment approach:

- **Type of Assessment:** distinguishes whether the approach is a dose-response assessment or whether it combines dose response and exposure information to perform a risk characterization.

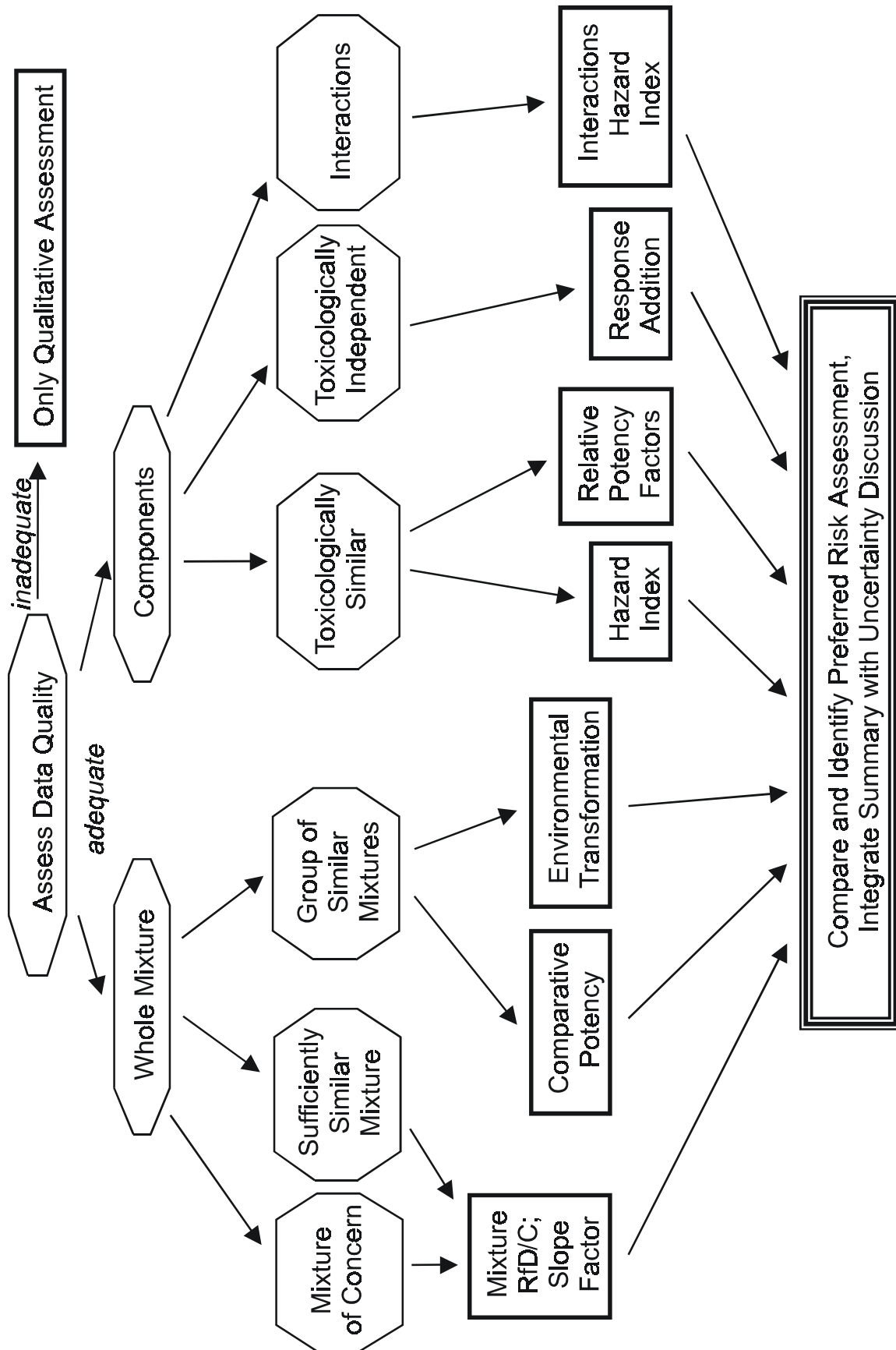


Figure 2-1. The different types of mixtures assessments based on the availability and quality of the data.
All possible assessment paths should be performed.

- Data Requirements: details the types and amount of data that are needed to carry out the procedure.
- Section(s): refers the user to sections of this document that provide greater detail on the approach.
- References: cites reports or publications in which the approach has been applied in practice or indicates that this is a new procedure.
- Strategy of Method: provides concise directions on how the calculations are performed.
- Ease of Use: gives a sense of how much effort, expertise, and data are required in order to apply the approach.
- Assumptions: lists the toxicologic or statistical assumptions that are inherently made when the data are treated by applying the approach; the user can then decide if the approach is appropriate for the available data.
- Limitations: suggests problems the user may encounter relative to data gaps or quality deficiencies, and statistical modeling requirements or goodness-of-fit issues.
- Uncertainties: indicates unknown elements of the analysis that should be considered and characterized in the presentation of the risk assessment (e.g., data are not available, mode of action is unknown, scientific judgments are made, exposures are not well characterized, extrapolations are made, etc.).

Following an assessment of data quality, the first major distinction addressed in Figure 2-1 is whether the type of available data is whole mixture data or mixture component information. This distinction points the risk assessor toward methods that are available for these specific types of data. Methods available for whole mixtures then depend on whether there is information directly available on the mixture of concern or only on sufficiently similar mixtures or groups of similar mixtures. Methods available for component data then depend on whether there are interactions data available or whether the components act with a similar mode of action or are toxicologically independent. In these cases, the outcome is a quantitative assessment with a complete risk characterization and uncertainty discussion presented.

Figure 2-1 is deceptively simple, however, as many of the issues that are represented in the diagram require the use of scientific judgment or data that may not be readily available. In addition, there will often be mixtures for which there exist both whole-mixture and component data, so that the choice of method will not be clear (for example, both epidemiologic data and component toxicity data exist for evaluation of health effects from exposure to chlorinated drinking water). Furthermore, the true toxicologic mechanism of action (see Section 2.2.3) is rarely known for a given mixture or even for most of its components; thus the judgments that are made of toxicologic similar action or independence of action, for example, will be uncertain. It is recommended, therefore, that the risk assessor implement several of the approaches that are practical and evaluate the range of health risk estimates that are produced.

2.2.3. Key Concepts

There are several concepts that must be understood in order to evaluate a chemical mixture (see Appendix B). The first is the role of toxicologic similarity which, in this document, is considered along a continuum of information. The term mode of action is defined as a series of key events and processes starting with interaction of an agent with a cell, and proceeding through operational and anatomical changes causing disease formation. “Mode” of action is contrasted with “mechanism” of action, which implies a more detailed understanding and description of events, often at the molecular level, than is meant by mode of action. The specific term *toxicologic similarity* represents a general knowledge about the action of a chemical or a mixture and can be expressed in broad terms such as at the target organ level in the body (e.g., enzyme changes in the liver). In this document, assumptions about toxicologic similarity are made in order to choose among risk assessment methods. In general, we assume a similar *mode of action* across mixtures or mixture components and, in some cases, this requirement may be relaxed to require that these chemicals act only on the *same target organ*.

The second key concept in understanding mixtures risk assessment is the assumption of similarity or, in contrast, independence of action. The term *sufficiently similar mixture* refers to a mixture that is very close in composition to the mixture of concern, such that differences in their components and their proportions are small; the risk assessor can then use the data from the sufficiently similar mixture to make a risk estimate about the mixture of concern. The term *similar components* refers to the single chemicals within a mixture that act by the same mode of action and may have comparable dose-response curves; the risk assessor can then apply a component-based approach that uses these characteristics to form the basis of the risk assessment. The term *group of similar mixtures* refers to chemically related classes of mixtures that act by a similar mode of action, have closely related chemical structures, and occur together routinely in environmental samples, usually because they are generated by the same commercial process; the risk assessor can use what is known about the shifts in chemical structure and relative potency of the components to perform a risk assessment. Finally, the term *independence of action* is defined as mixture components that cause different kinds of toxicity, or effects in different target organs; the risk assessor may then combine the probabilities of toxic effects for the individual components.

Another key concept for this document is the understanding of language referring to toxicologic interactions, which is defined here as any toxic responses that are greater than or less than what is observed under an assumption of *additivity*. The term *additivity* is used when the effect of the combination of chemicals can be estimated directly from the sum of the scaled exposure levels (dose addition) or of the responses (response addition) of the individual components. There are a myriad of terms (see Appendix B, Table B-2) that represent various

kinds of interaction effects (e.g., inhibition, antagonism, masking). The most common and general of these refer to effects that are greater than additive (i.e., synergistic) or less than additive (i.e., antagonistic).

2.2.4. Qualitative Assessments

In Figure 2-1, an evaluation of the data may lead the user to decide that only a qualitative analysis should be performed. This generally occurs in cases where data quality is poor, there are inadequate quantitative data available, data on a similar mixture cannot be classified as “sufficiently similar” to the mixture of concern, exposures cannot be characterized with confidence, or method-specific assumptions about the toxicologic action of the mixture or of its components cannot be met. When this occurs, the risk assessor can still do a qualitative assessment that characterizes the potential human health impacts from exposure to that mixture. Such a risk characterization should discuss each element of the risk assessment paradigm, including available information on the mixture itself, on its components, and on potential interactions among the components. Any information on fate and transport of the mixture that would affect its final composition at the time of exposure should be noted.

2.2.5. Defaults

The development of a risk assessment for a chemical mixture will generally involve the examination of complex exposures and toxicities and the application of specific methods as well as scientific judgment. This process necessarily involves a thorough examination and discussion of the uncertainties, limitations, and assumptions inherent in exposure assessment, fate and transport, uptake and pharmacokinetics, and the magnitude and nature of toxicity and toxicant interactions. Because of the complexity of considerations that must be undertaken to develop a chemical mixtures health risk assessment, it is not practical to recommend a clear listing of default procedures that covers all cases. In many cases, information gaps will be too substantial to allow use of defaults, so that only a qualitative risk assessment can be performed. Nonetheless, for some restricted situations, default values and methods can be recommended. This section outlines the philosophy underlying their choice.

For low exposure levels when no interactions information is available, default methods using an additivity assumption are given. For the component chemicals in a mixture that show dissimilar toxicity, response addition (Sections 2.6.2, 4.1, and 4.5) is recommended. For the component chemicals that show similar toxicity, dose addition (Sections 2.6.1, 4.1, 4.2, and 4.4) is recommended. Under dose addition, the general procedure is to scale the doses of the components by their relative potency and add the scaled doses together; the mixture response is then estimated for the combined dose. Under response addition, the general procedure is to first

determine the risks per the exposure for the individual components; the mixture risk is then estimated by adding the individual risks together. These processes are fundamentally different and require different assumptions of the data in order for them to be used appropriately. Finally, if interactions data are available, the default recommendation is that they be incorporated into the risk assessment by using the interaction-based Hazard Index (HI) (Sections 2.6.3, 4.1, and 4.3).

Dose addition is the default approach in situations where the dose for each individual component is at a level at which effects are not expected to occur, be observable, or be of concern; however, when the doses are combined, effects of concern may be expected or observed in response to the higher dose level of the mixture. A method based on dose addition that has been used most often by EPA is the HI, where $HI < 1$ indicates a mixture exposure of no significant concern (U.S. EPA, 1989a). True dose addition is applied by scaling the potencies of all the components in the mixture with the same mechanism of action to an index chemical, adding the scaled doses together to give the equivalent dose in terms of the index chemical, and using the index chemical's dose-response curve to estimate the response for the equivalent total mixture dose. Dose addition is different from response addition because two assumptions are made: that all of the components have similar uptake, pharmacokinetics, and toxicologic processes; and that the dose-response curves of the components have congruent or similar shape (Teuschler and Hertzberg, 1995). This means that, for equal effects, the dose of one component is a constant multiple of the dose of a second component.

The interaction-based HI is the default approach for using interactions data to modify simple dose addition. This approach uses binary interactions data for the components of the mixture to modify the HI. The factors that are used include the interaction magnitude at low doses, the toxicity of each component relative to each other component, the weight of evidence of the interactions data, and the relative proportions of the components in the mixture.

Response addition is the default approach when the component chemicals are functionally independent. It is most often applied when an effect that is of concern is expected to be present at low dose levels for each of the component chemicals, even though it is highly unlikely to be observable at these low levels in either epidemiologic or toxicologic studies; the mixture risk is then usually approximated by the sum of the individually low risks of the independently acting component chemicals. For example, response addition has often been used for the risk assessment of mixtures of carcinogens (Gaylor et al., 1997; U.S. EPA, 1989a). Response addition is different from dose addition in that it does not assume similar kinetics or a similar mode of action and does not assume that the dose-response curves have similar shape. It assumes that the components of the mixture are functionally independent of one another at low exposure levels (Mumtaz and Hertzberg, 1993), so that the risks may be added together (see Section 4.5 for details on interpretation and calculation). Because response addition does not

require a similar mode of action across the chemicals in the mixture, it allows for combining risks across chemicals even if they have different types of endpoints. An example is the combined risk of any kind of reproductive toxicity for a set of chemicals with different modes of action.

2.3. DATA QUALITY ASSESSMENT

The first consideration in Figure 2-1 is the assessment of data quality relative to its relevancy, completeness, quantitative nature, and certainty in three areas: exposure information, health effects information, and information on interactions. Table 2-1 presents a classification scheme for assessing the quality and nature of the available mixtures data. Consideration of the factors presented in Table 2-1 can be used to guide the risk assessor through Figure 2-1. This evaluation can assist the decision of whether to quantify the risk (the first step in Figure 2-1), and can be included in a discussion of overall quality of the risk assessment. Usually a classification of “FAIR” or better is required for quantitative risk assessment. For example, a “GOOD” classification for each of exposure information, health effects information and information on interactions would lead the risk assessor to consider the data quality to be adequate for quantification, with good data available for both the exposure and toxicity aspects of the mixture of concern. Figure 2-1 would then guide the risk assessor to perform a risk assessment directly on the mixture of concern by calculating, for example, a toxicity value for the mixture, such as a Reference Dose (RfD) or slope factor. A “POOR” classification for one or more of these categories would likely lead the risk assessor to decide that data quality was inadequate; in this case, Figure 2-1 directs the risk assessor to perform only a qualitative risk assessment. With “FAIR” information on each of exposure, health effects, and interactions, the risk assessor would conclude that data quality was adequate to estimate both the exposure and toxicity of the components of the mixture, and furthermore to use the available interactions data on the components in the assessment. Under these conditions, Figure 2-1 indicates that an interaction-based HI approach would be appropriate. It is the purview of the risk assessor to decide at what point the validity of the risk assessment is compromised by the data quality to such a degree that only a qualitative assessment should be performed.

2.3.1. Quality of Exposure Information

Exposure information ideally includes all data needed to characterize the human exposure to the mixture of concern from the point of environmental release to the point of human intake. There are several details needed to quantify exposure to chemical mixtures; these include:

Table 2-1. Classification scheme for the quality of available mixtures data^a	
Exposure Information^b	
GOOD	– Monitoring information either alone or in combination with modeling information is sufficient to accurately characterize human exposure to the mixture or its components. – Modeling information is sufficient to reasonably characterize human exposure to the mixture or its components.
FAIR	– Exposure estimates for some components are lacking, uncertain, or variable. Information on health effects or environmental chemistry suggests that this limitation is not likely to substantially affect the risk assessment. – Not all components in the mixture have been identified, or levels of exposure are highly uncertain or variable. Information on health effects or environmental chemistry is not sufficient to assess the effect of this limitation on the risk assessment.
POOR	– The available exposure information is insufficient for conducting a risk assessment.
Health Effects Information	
GOOD	– Full health effects data are available and relatively minor extrapolation is required. – Full health effects data are available but extensive extrapolation is required for route or duration of exposure or for species differences. These extrapolations are supported by pharmacokinetic considerations, empirical observations, or other relevant information.
FAIR	– Full health effects data are available, but extensive extrapolation is required for route or duration of exposure or for species differences. These extrapolations are not directly supported by the information available. – Certain important health effects data are lacking and extensive extrapolations are required for route or duration of exposure or for species differences.
POOR	– A lack of health effects information on the mixture and its components in the mixture precludes a quantitative risk assessment.
Information on Interactions	
GOOD	– Assessment is based on toxicologic data on the mixture of concern. – Assessment is based on data on a sufficiently similar mixture.
FAIR	– Quantitative interactions of all components are well characterized. – The assumption of additivity is justified based on the nature of the health effects and on the number of component compounds.
POOR	– Interactions information is inadequate, an assumption of additivity cannot be justified, and no quantitative risk assessment can be conducted.

^aSee text for discussion of sufficient similarity, adequacy of data, and justification for additivity assumptions.

^bSee the Agency's guidelines for exposure assessment (U.S. EPA, 1992) for more complete information on performing exposure assessments and evaluating the quality of exposure data.

- Concentration of the chemical mixture in the medium/media of concern at the point(s) of human contact
- The duration and frequency of exposure should be developed from repeated measurements or validated models of environmental fate in media to which individuals are exposed, as well as human activity pattern data. The media concentrations should be determined at the points of human exposure. If the exposure data are limited, the analyst should address the degree to which the data

represent the environmental chemical mixture over space and time.
Environmental transformation of the mixture over time is a key concern.

- Analytic chemistry

The analyst should consider both the accuracy and reliability of the measurement techniques and determine if all of the components have been identified (i.e., are there unidentified components of the mixture?). The analyst should also determine if the key environmental reactions have been identified and reaction rates measured (e.g., environmental half-life) that govern the fate of the mixture. If components of the environmental mixture have not been detected analytically, the analyst should describe if and how they were included in the assessment (e.g., the compounds were assumed to be present at one-half the detection limit).

- Uptake from the environment

The analyst should examine the bioavailability of the mixture for the medium and route of concern. The ideal data set would be derived from well-conducted studies that measure either the entire mixture or all the components in the pertinent exposure media and over the timeframe of concern. (The ideal data may be derived from accurate analytic measurements at points of human contact or from validated environmental fate models.) The magnitude of the human exposure would be measured or modeled on the basis of human activity patterns. Finally, the bioavailability of the mixture or the components would be known. Unfortunately, a complete data set is rarely available. The analyst should identify (and perhaps quantify) uncertainty based on imperfect analytic methods (e.g., some constituents may not be characterized by the analytic technique that represents the current state of the science), extrapolations between concentrations at measurement points and points of human exposure, incompletely understood transformation reactions to the mixture in the environment, and bioavailability. Each of these uncertainties in the risk assessment should be discussed and accounted for in the final risk characterization.

2.3.2. Quality of Health Effects Information

Health effects information includes both hazard identification and dose-response data on the complex mixture, a similar mixture, or the components of the mixture. The best data would be human epidemiologic or human clinical data directly on the complex mixture for which the health effects of concern are causally linked to the mixture exposure and a dose-response relationship can be established for the exposure route of interest. Unfortunately, such high-quality direct information is rarely available, so the risk assessor usually performs one or more extrapolations. Examples of such extrapolations include using animal data to project potential human health effects, using inhalation data to predict risks from oral exposure, using component data to estimate risks for the complex mixture, and using data from short-term human clinical

studies or subchronic animal bioassays to project human health risks from chronic exposure. Each of these extrapolations introduces uncertainty into the risk assessment that should be discussed and accounted for in the final risk characterization.

2.3.3. Quality of Interactions Information

Interactions information includes any data indicating that the toxicologic action of the complex mixture is greater than or less than what might be expected from exposure to a collection of individual components of the mixture. Thus, human or animal data directly on the whole mixture implicitly provides interactions information for use in risk assessment. However, since such data are rarely available, the risk assessor must often rely on component information, the vast majority of which is laboratory toxicity data on binary combinations of chemicals (Teuschler and Hertzberg, 1995). The quality of interactions data, whether it be data on the complex mixture, a sufficiently similar mixture, or simple combinations of the components, can be judged according to the strength of evidence for three criteria. First, there should be adequate toxicity data that not only provide information on dose response, but also on the mechanism of action for the mixture. Second, interactions data should be for the same route of exposure as the mixture of concern. Furthermore, when data on several different component mixtures are evaluated, these data should be from comparable studies, such as the same species, same endpoint of concern, similar laboratory conditions, or comparable study duration. Finally, observed interactions data that are usable for risk assessment purposes should be toxicologically significant (i.e., show definite adverse effects). The strength of the evidence for each of these criteria should be discussed and accounted for in the final risk characterization.

2.4. CHEMICAL MIXTURE EXPOSURE ASSESSMENT ISSUES

While this guidance document is intended to serve risk assessors primarily by informing them of dose-response and risk characterization methods associated with exposures to chemical mixtures, the purpose of this section is to highlight additional exposure issues of a *general* nature that should be considered when developing a risk assessment for chemical mixtures. The issues presented in this section should be considered in addition to those normally followed in an exposure assessment. The Agency's primary guidance in this area is the Exposure Assessment Guidelines (U.S. EPA, 1992); however, that document primarily focuses on issues pertaining to single-chemical exposures. Other, more specific exposure assessment issues involving multiple chemicals will be discussed by the Agency more comprehensively in separate future efforts (e.g., the EPA's Risk Assessment Forum is developing a cumulative risk assessment framework as this guidance goes to press). While there are other important issues related to exposures to chemical

mixtures, three critical areas will be discussed briefly here: environmental fate, temporal patterns of exposure, and routes of exposure.

The wide diversity in mixture compositions and site characteristics precludes any recommendation for a single approach for site-specific modification of the mixture assessment. Through examples, some steps that should be considered can be articulated. The example in Section 3.4 demonstrates some of the considerations that should be part of such a modification. Other modifications based on the exposure and mixture characteristics are encouraged, as long as they are clearly described and supported with plausible concepts and empirical measurements. Clearly, the analyst should report the significance of any assumptions utilized as well as the potential uncertainty and variability associated with the exposure modifications developed for the risk assessment.

2.4.1. Environmental Fate and Transport

The composition and quantity of a mixture of chemicals may change after release into the environment. The environmental fate of chemical mixtures released into the environment can be conceptualized as being composed of three *interrelated* components: (1) transport through an individual compartment (e.g., atmospheric dispersion); (2) transfer between environmental compartments (i.e., partitioning); and (3) transformation mediated by biological, chemical, or physical processes (e.g., weathering) (Crawford-Brown, 1997, Chapter 2). Even though the environmental processes that occur within these three components of environmental fate are not unique to chemical mixtures, the analyst should assess compositional and quantitative changes that may occur to the chemical mixture of interest in the environment (particularly with respect to the time from release to exposure), and the impact these will have on exposure and toxicity.

This is particularly important when considering the appropriateness or relevance of an analytic measurement of quantity or composition of a chemical mixture; the analyst needs to consider the possible changes to the mixture between the time the measurement was conducted and the time over which exposures are expected to occur. These environmentally mediated changes are also important when comparison is made in the assessment to the dose response exhibited by either a sufficiently similar whole mixture (e.g., comparison of the dose response of the commercial mixture that has been toxicologically tested to that of the environmental mixture) or mixture components. The concept of *sufficient similarity* is not discussed in the 1986 mixtures guidelines (U.S. EPA, 1986, 1987) (Appendix A). Common sense dictates that *sufficient similarity* entails the assumption that the toxicologic consequences of exposure to the two mixtures (i.e., the mixture of concern and the mixture on which data are available) will be identical or at least indistinguishable from one another. In practice, some degree of chemical similarity or at least an understanding of how chemical differences between the mixtures affect

toxicological activity is required. The acceptability of a surrogate, given the degree of accuracy desired in the risk assessment, should be identified in the analysis.

When the effects of such environmental processes cannot be directly measured or modeled on the mixture of interest, there is potential for substantial error in the risk assessment. The risk assessment can sometimes be modified by knowledge of the process that is generating the mixture exposure, or by information on the original mixture chemicals along with the geochemical and biochemical processes operating during their transport and over time. The degree to which environmental fate alters the exposure or the dose response changes a basic assumption of risk assessment of chemical mixtures, that of sufficient similarity. Under some circumstances, sufficiency of similarity may be gauged by the gradient of costs (monetary or environmental) of misjudging similarity, although such analyses will not be discussed here.

Whenever the mixture risk assessment is based on chemical component information and the mixture composition cannot be fully identified, the uncertainty and possible bias in the resulting risk assessment should be clearly described. Attention should also be given to the persistence of the mixture in the environment as well as to the variability of the mixture composition over time or from different sources of emissions. The assessment should also discuss methods for improving the assessment, including gathering of more data as well as employing other measurement or extrapolation techniques.

2.4.1.1. Transport Through an Environmental Compartment

Transport of a chemical mixture through the environmental compartments of air, soil, and water will depend upon the physical and chemical properties of the individual components or the unique properties of the chemical mixture (e.g., nonaqueous-phase liquids [NAPLs]) and the environmental medium. There are a number of examples of changes in composition or quantity of a chemical mixture as a result of environmental fate. The changes in the quantities and concentrations of chemical disinfectant by-products (occurring in chemically disinfected drinking water over time) during transport through the drinking water distribution system provide an example of the changes that can occur to a mixture during transport through an environmental compartment.

2.4.1.2. Intercompartmental Transfer Between Environmental Compartments

All components of a chemical mixture may not be transferred between environmental compartments at the same rate. Once released to the environment, a mixture of chemicals may be partitioned on the basis of the physical/chemical properties of each component of the mixture and the condition of the microenvironment into which the components are partitioned.

Selective movement of components can occur primarily during transport between soil, air, or water environments. For example, volatilization from the soil surface compartment to the atmospheric compartment could be important initially for the more volatile compounds in the mixture. Volatilization from dry soil surfaces is dependent on both the vapor pressure (more volatile compounds will volatilize more readily) and the ability of a compound to adsorb to soil. Volatilization from moist soil surfaces is driven by the Henry's Law constant at steady state (volatilization increases with a larger Henry's Law constant) and, as with dry soil surfaces, the ability of a compound to adsorb to the soil. Because the Henry's Law constant is defined as the ratio of a compound in air to that in water, compounds with either a high vapor pressure or compounds that have a low vapor pressure together with a low water solubility may volatilize from both moist soil and water surfaces. The rate at which a compound can volatilize from the soil surface may be attenuated if that compound is also able to adsorb strongly to soil particles. Compounds that adsorb strongly to the soil may also be physically entrained in the air as dust or moved to aquatic environments via sediment runoff. Compounds that do not adsorb strongly to the soil may leach readily through the soil column to groundwater systems if processes such as volatilization and biodegradation do not occur rapidly enough. (There are exceptions, such as where some vapor-phase pollutants in stack emissions adsorb to particulates.) The extent of soil adsorption is generally based on the organic content of the soil, although some compounds (those with a positive charge) can also adsorb to clays. A soil adsorption coefficient is defined in terms of the soil organic carbon and can be used to estimate the ability of a particular compound to leach into the soil column. The more volatile components of a chemical mixture in soil may volatilize over a several-year period and no longer be present. A risk assessment based only on the original mixture composition could then overestimate the long-term risk if the volatile chemicals were the primary toxicants. Adjustments based on other factors such as exponential decay models calibrated for the soil composition being assessed might improve the risk estimate.

The analyst should also consider differential transfer of chemicals comprising a mixture between abiotic and biotic compartments and between two different biotic compartments. For example, certain dioxin congeners released from the stacks of combustion sources appear to be selectively taken up and retained in plant tissues (Lorber et al., 1996; 1998). The relative proportions of dioxin congeners in the mixture to which humans and grazing animals are exposed through the consumption of these contaminated plants vary considerably from the original congener mixture released to the environment. The proportions of dioxin congeners in human exposures that result from consumption of the tissues of the grazing animals (e.g., beef cattle) will differ from the proportions released from the stack as well as those in the contaminated plants.

2.4.1.3. Transformation of a Chemical Mixture or Individual Compound Into Degradation Products

In the environment, chemical mixtures may arise or change as a result of transformation. If the various compound/s are susceptible to degradation via photolysis, hydrolysis, or biodegradation (both aerobic and anaerobic), both alteration of the profile of the original compounds in the mixture and changes in the quantity of the mixture present are possible. The processes acting to change the profile of a mixture may be affected by the point of release of the mixture (i.e., the profile from a mixture directly released to a lake may be different from that from the same mixture following long-range atmospheric transport). Transformation reactions that may differentially affect mixtures components in air, soil, and water are presented below, followed by an example using the transformation of toxaphene.

- Atmosphere: Compounds can be transformed by direct photolysis, if the compound is able to absorb light in the visible region of the spectrum, and/or by reaction with reactive photochemically generated hydroxyl radicals, nitrate radicals, and ozone (Atkinson, 1994). Reaction with hydroxyl radicals is expected to be the major degradation process in the troposphere for most molecules, and the rate of this reaction depends primarily on the chemical structure (Atkinson, 1994). Unsaturated compounds also are expected to react quickly with nitrate radicals and ozone.
- Soil: Compounds can be transformed through aerobic and anaerobic biodegradation at the soil surface. Aerobic biodegradation is controlled by concentrations of oxygen and nutrients; compounds susceptible to anaerobic biodegradation may be transformed in anaerobic microsites, which may be found within the soil column and when the soil is flooded.
- Water: Susceptible compounds may be transformed through hydrolysis (e.g., structures such as amides, alkyl halides, carbamates, and phosphoric acid esters [Lyman et al., 1990] are particularly vulnerable), direct photolysis at the water surface, and aerobic biodegradation.

The assessment of environmentally degraded or “weathered” toxaphene, previously the most heavily used pesticide in the United States, exemplifies the concerns of transformation as well as other environmental fate processes when developing a chemical mixtures risk assessment. Toxaphene is a formulation of multiple ingredients. The relative amounts of these components and their character change after toxaphene is released to the environment and the original components of the mixture are exposed to differential partitioning and transformation processes in air, water, and soil environments (U.S. EPA, 1997b).

- Toxaphene congeners are generally biologically degraded under anaerobic conditions through reductive dechlorination. Anaerobic degradation rates in soils and sediments are expected to be determined largely by qualities of the original component molecules and the environment's potential to interact and change the molecules' structure (Fingerling et al., 1996; Smith and Willis, 1978). The stability of reaction products, whether in soil or sediment, seems to depend on the position of the various chlorine atoms.
- Under aerobic conditions toxaphene degrades slowly, if at all (Parr and Smith, 1976; Bidleman et al., 1981; Mirsatari et al., 1987; Nash and Woolson, 1967).
- In general, the lower chlorinated toxaphene congeners are more easily vaporized than are the higher chlorinated congeners (Seiber et al. [1979] showed soil surface enrichment of the less volatile, more chlorinated compounds through GC analysis); however, both can be atmospherically transported.
- Toxaphene, particularly the more volatile components, may be transported far from the initial source by long-range atmospheric transport processes.
- Once deposited in water, the higher chlorinated congeners can bioaccumulate in the food chain because of their lipophilicity.

The composition of "weathered" toxaphene samples may be different, depending on the environmental processes to which the original agent was exposed. For example, toxaphene extracted from an anaerobic soil does not resemble that from an aerobic soil, and toxaphene detected in an air sample from the Arctic does not resemble the toxaphene residue obtained from the blubber of an Arctic seal. Site-specific consideration of the partitioning and transformation processes is needed for different environments. The resulting changes in chemical composition of the original mixture over time will affect the toxicity of the mixture.

For another example, when the primary change to a mixture is believed to be the degree of halogenation or other substitution, some adjustment of the estimated exposure or toxic potency may be possible. One example (discussed in Section 3.4) concerns combinations of PCBs, for which EPA has developed specific methodology to alter the toxic potency on the basis of site-specific environmental factors.

2.4.2. Importance of the Exposure Sequence for Multiple Chemicals

The order in which chemical exposures occur and the time between exposures to different chemical agents may affect the nature of the response to the chemical insult. For example, the sequence or pattern of exposure is important for compounds that have been described as initiators and those described as promoters of carcinogenicity. There is evidence to suggest that exposure to certain compounds results in an irreversible change in the affected cells and progeny (the cell is said to be initiated). When the initial exposure is followed by repeated doses of a second chemical agent (i.e., the promoter), tumors occur. In the absence of either the initiator or the

promoter, or if the order is reversed, tumors do not occur. An example of an initiator-promoter sequence is the application of a PAH (initiator) (e.g., benzo[b]fluoranthene) followed by repeated applications of 12-o-tetradecanoyl phorbol-13-acetate (TPA) to the skin of shaved mice (Amin et al., 1985).

2.4.3. Routes of Exposure

In environmental health risk assessments, analysts typically consider three routes of human exposure: oral, dermal, and inhalation. Differences in the properties of the cells that line the surfaces of the gastrointestinal tract, the skin, and the air pathways and lungs may result in different intake patterns of chemical mixture components depending on the route of exposure. Additionally, chemicals in a mixture may partition to contact media differently, resulting in different potential routes of exposure (see Section 2.4.1). In chemical mixtures risk assessment, the issue becomes how and when to combine routes. EPA is still developing approaches for this. EPA (1998c) recommends that route-to-route conversion should be attempted only for dermal exposures at this time. Adequate inhalation-to-oral conversion methods for steady-state conditions have not yet been developed. A general outline of the oral-to-inhalation extrapolation process and a discussion of route-to-route extrapolation issues can be found in Gerrity and Henry (1990) and in EPA's Reference Concentration methodology document (U.S. EPA, 1994a). Until such methodology is developed, inhalation and oral risk characterization should be carried out separately. The assessor should note, however, that total risk from the mixture could be underestimated by not combining all routes of exposure, because the total exposure is not characterized and the chemical interactions may not be considered.

Multiple-route exposures can be combined in two different ways: summing the absorbed daily doses or summing the (external) oral equivalent daily doses. Both approaches require an estimate for the oral absorption fraction, but the latter is adopted here as it is simpler for consideration with standard toxicity comparison values based on ingestion (e.g., RfD).

A number of factors might contribute to differences in toxicologic effectiveness between oral and dermal exposures at equal dosages. The most obvious relates to differences in absorption rates between the two routes. Other potential contributing factors include differing sensitivity of absorption sites to damage and differences in toxicokinetics (i.e., distribution, metabolism, elimination) between exposure routes. Ideally, the conversion from dermal to equivalent oral dose would be based on experimentally derived values that characterize the relationship between the doses that produce a particular toxicity by each of the different routes. In practice, however, the conversion usually will be based on absorption factors because of a general absence of appropriate data.

2.4.4. Exposure Assessment Summary

This section summarizes a few important concepts related to chemical mixtures exposure assessment. Once a chemical mixture is released to the environment, its concentration and composition may change through partitioning into abiotic and biotic compartments and through transformation mediated by the environment and biota. The physical/chemical properties of each component of the mixture (or the properties of the mixture as a whole) and the condition of the microenvironment into which the components are partitioned may change the magnitude and the routes of human exposure. Partitioning and transformation of the mixture components will affect the routes of exposure. Ideally, chemical mixture exposures through different routes can be integrated through measurement data or a validated physiologically based pharmacokinetic (PBPK) model; at this time, approaches are still evolving, particularly for combining inhalation and oral exposures. The sequence of exposures to different chemical agents is clearly important for some responses. A number of other issues will be deferred for later discussion by the Agency; these include chemical mixtures with intrinsically unique properties (e.g., NAPLs), mass balance within chemical mixtures assessments, assessing risk of unidentified components of chemical mixtures, measurement issues, and component bioavailability.

2.5. DATA AVAILABLE ON WHOLE MIXTURES

Whenever possible, the preferred approach to the health risk evaluation of chemical mixtures is to perform the assessment using health effects and exposure data on the whole mixture. Such data include human epidemiologic, clinical, or occupational studies; animal studies on the complex mixture; or in vitro data on the complex mixture. Figure 2-1 shows that the whole-mixtures data can then be divided into subsets of data directly on the mixture of concern, data on a sufficiently similar mixture, or data on a group of similar mixtures. This guidance document discusses these situations and offers some examples of how to approach a whole-mixture health risk assessment.

2.5.1. Data Available on the Mixture of Concern

Exposure and toxicity data directly on the mixture of concern are most likely to be available for highly complex mixtures, such as coke oven emissions, which are generated in large quantities and associated with or suspected of causing adverse health effects. The evaluation of such a mixture requires scientific judgment regarding the stability of the mixture in the environment and the linkage of the observed human health effect to the mixture exposure. Toxicity data obtained from concentrates or extracts of the original mixture of concern may not be predictive of human toxicity to the original mixture. Such data are more properly handled using procedures developed for toxicologically similar mixtures (Sections 2.5.3, 3.3).

2.5.1.1. User Fact Sheet: Mixture of Concern RfD/C or Slope Factor

The user of this guidance document can use Figure 2-1 to determine if data are available directly on the mixture of concern. Then a procedure is suggested for estimating either a cancer slope factor or a reference dose/concentration (RfD/C), as encapsulated in the following user-information fact sheet.

Approach:	Mixture of Concern RfD/C or Slope Factor
Type of Assessment:	Dose-Response Toxicity Value
Section(s):	3.1, 3.2
References:	Examples can be found on IRIS (U.S. EPA, 2000a).
Data Requirements:	Toxicity data are available on the mixture of concern. Examples of such data are human epidemiologic data from an occupational setting, human data from a clinical study, or animal toxicology data on the complex mixture.
Strategy of Method:	Estimate dose-response toxicity value directly from data on complex mixture of concern, using the same procedures as those used for single chemicals.
Ease of Use:	Calculations are simple.
Assumptions:	Composition of the test mixture is functionally the same as what is found in the environment. Test data are adequate to account for all sensitive endpoints.
Limitations:	Data are rarely available.
Uncertainties:	Scientific judgments of the chemical composition of the mixture; toxicologic relevance of the laboratory data to the environmental mixture.

2.5.2. Data Available on a Sufficiently Similar Mixture

If data are not available on the mixture of concern, the risk assessment may be based on data on a sufficiently similar mixture. A mixture is sufficiently similar to the mixture of concern when its components are not very different and are contained in about the same proportions as the mixture of concern. In addition, if information exists on differences in environmental fate, uptake and pharmacokinetics, bioavailability, or toxicologic effects for either of these mixtures or their components, it should be considered in the determination of sufficient similarity. If such data are available, an attempt should be made to determine if significant and systematic differences exist between the chemical mixtures. If no significant differences are noted, then a risk assessment may be performed using data on the sufficiently similar mixture as a surrogate for the mixture of concern.

2.5.2.1. User Fact Sheet: Sufficiently Similar Mixture RfD/C or Slope Factor

The user of this guidance document can use Figure 2-1 to determine that the data available are on a mixture that is sufficiently similar to the mixture of concern. Then a procedure is suggested for estimating either a cancer slope factor or a reference dose/concentration (RfD/C), as encapsulated in the following user-information fact sheet.

Approach:	Sufficiently Similar Mixture RfD/C or Slope Factor
Type of Assessment:	Dose-Response Toxicity Value
Section(s):	3.1, 3.2
References:	New procedure.
Data Requirements:	Toxicity data are available on a mixture that is judged as sufficiently similar to the mixture of concern in the environment. No data are available on the mixture of concern. Examples of such data are human epidemiologic data from an occupational setting, human data from a clinical study, or animal toxicology data on the complex mixture.
Strategy of Method:	Estimate dose-response toxicity value using data on the sufficiently similar mixture as a surrogate for data on the mixture of concern, using the same procedures as those used for single chemicals.
Ease of Use:	Calculations are simple.
Assumptions:	Composition of the sufficiently similar mixture is functionally the same as what is found in the environment. Test data are adequate to account for all sensitive endpoints. Similarity judgment across the mixtures must be made and supported.
Limitations:	Availability of data is limited.
Uncertainties:	Scientific judgments of sufficient similarity, chemical composition and stability of the two mixtures; toxicologic relevance of the laboratory data to the environmental mixture.

2.5.3. Data Available on a Group of Similar Mixtures

In some cases, data are available on a group of similar mixtures that are known to be generated by the same commercial process or emissions source but that vary slightly in composition depending on factors such as time since emission, environmental transformation, or geographic location of emission sources. Data are then available on several mixtures with approximately the same components but with slightly different component exposure levels, so that the likely range of compositional variation is covered. Thus, risk assessors can use toxicity and exposure data that exist on the group of similar mixtures and extrapolate in order to perform a risk assessment on the less well-studied or environmentally transformed mixtures that belong to that same group.

2.5.3.1. User Fact Sheet: Comparative Potency

The user of this guidance document can use Figure 2-1 to determine that the data available are on a group of similar mixtures. Then a procedure is suggested for using a comparative potency approach to estimating a cancer slope factor, as encapsulated in the following user-information fact sheet.

Approach:	Comparative Potency
Type of Assessment:	Dose-Response Toxicity Values for Cancer, Genetic Toxicity
Section(s):	3.1, 3.3
References:	Used for combustion mixtures (Lewtas, 1985, 1988; Nesnow, 1990).
Data Requirements:	Method requires short-term data on several similar mixtures including the mixture of concern, and at least one data point from a chronic in vivo study on one of these mixtures. Examples of such data are in vitro mutagenicity assays and chronic rodent bioassays.
Strategy of Method:	Estimate dose-response value using relationships across similar mixtures and similar assays to extrapolate to a value for the mixture of concern.
Ease of Use:	Calculations involve some statistical modeling and toxicologic judgment. Method is data intensive with short-term assay data required.
Assumptions:	Assumes the potency change for similar mixtures across assays is the same for all similar mixtures. Test data are adequate to account for all sensitive endpoints. Similarity judgment across the mixtures must be made and supported.
Limitations:	Availability of data is limited.
Uncertainties:	Scientific judgments of sufficient similarity relative to chemical composition and toxicologic activity of the mixtures.

2.5.3.2. User Fact Sheet: Geographic Site-Specific Assessments

The user of this guidance document can follow Figure 2-1 to determine that the data available are on a group of similar mixtures. Then a procedure is suggested for estimating risk from exposure to the mixture by using a geographic site-specific assessment, as detailed in the following user-information fact sheet.

Approach:	Geographic Site-Specific Assessment
Type of Assessment:	Risk Characterization for Any Toxic Endpoint
Section(s):	3.1, 3.4
References:	Used for cancer assessment of PCBs (U.S. EPA, 1996c)
Data Requirements:	Method requires both toxicity and exposure data on the mixture's components.
Strategy of Method:	Toxicity data on the commercial mixture are used to estimate a range of toxicity values that are then adjusted for alterations in the mixture's composition because of environmental factors to produce a risk estimate for the total mixture.
Ease of Use:	Complicated to use. Data intensive.
Assumptions:	Requires the user to make assumptions about the fate and transport of groups of chemicals.
Limitations:	Some data restricted by similarity. Restricted to specific conditions. Limited by data quality.
Uncertainties:	Scientific judgment of fate and transport. Accuracy of exposure data.

2.6. DATA AVAILABLE ON MIXTURE COMPONENTS

If data are not available on an identical or reasonably similar mixture, the risk assessment may be based on the toxic or carcinogenic properties of the components in the mixture. When quantitative information on toxicologic interaction exists, even if only on chemical pairs, it should be incorporated into the component-based approach. When there is no adequate interactions information, dose- or risk-additive models are recommended. The primary criterion for choosing between dose addition and response addition is the toxicologic similarity among the chemicals in the mixture. This decision should be based on information about the toxicologic and physiologic processes involved, the single-chemical dose-response relationships, and the type of response data available. The risk assessment using component data should then begin with selection of the most appropriate concept for the chemicals in the mixture.

2.6.1. Toxicologic Similarity and Dose Addition

In the simplest terms, chemicals can be considered as dose additive if each chemical can be thought of as a concentration or dilution of every other chemical in the mixture. The chemicals are assumed to behave similarly in terms of the primary physiologic processes (uptake, metabolism, distribution, elimination) as well as the toxicologic processes. The mathematical description of dose addition requires a constant proportionality between the effectiveness of the two chemicals. Three component methods that are based on dose addition are discussed in this document: the HI, the Relative Potency Factor (RPF) method, and the Toxicity Equivalence Factor method, which is a special case of the RPF method. They differ in the required knowledge about toxic mechanism and in the extent over which toxicologic similarity is assumed. In each method, the exposure levels are added after being multiplied by a scaling factor that accounts for differences in toxicologic potency.

2.6.1.1. User Fact Sheet: Hazard Index

The user of this guidance document can follow Figure 2-1 to determine that the data available are on the components of the mixture of concern and that there is evidence of toxicologic similarity of the components. Then a procedure is suggested for estimating a Hazard Index, an indication of risk from exposure to the mixture, as encapsulated in the following user-information fact sheet.

Approach:	Hazard Index
Type of Assessment:	Risk Characterization for Any Toxic Endpoint
Section(s):	4.1, 4.2
References:	Used in Superfund site assessments (U.S. EPA, 1989a).
Data Requirements:	Method requires both toxicity and exposure data on the mixture's components. Good dose-response data are needed, such as what is available on IRIS (U.S. EPA, 2000a).
Strategy of Method:	Scale individual component exposure concentrations by a measure of relative potency (typically, divide by a Reference Dose/Concentration [RfD/C]) for components with a similar mechanism-of-action. Add scaled concentrations to get an indicator of risk from exposure to the mixture of concern.
Ease of Use:	Easy to calculate.
Assumptions:	Applies dose addition, which carries with it assumptions of same mode of action and similarly shaped dose-response curves across the components. The "common mode-of-action" assumption can be met by using a surrogate of same target organ.
Limitations:	Exposure data should be at relatively low levels (near no-adverse-effect levels) at which interaction effects are not expected. RfD/C values across components vary in their uncertainty, so other measures of potency may be more appropriate.
Uncertainties:	Similarity of mechanism-of-action. Accuracy of exposure data.

2.6.1.2. User Fact Sheet: Relative Potency Factors

The user of this guidance document can follow Figure 2-1 to determine that the data available are on the components of the mixture of concern and that there is evidence of toxicologic similarity of the components. Then a procedure is suggested for estimating risk from exposure to the mixture by using Relative Potency Factors, as encapsulated in the following user-information fact sheet.

Approach:	Relative Potency Factors
Type of Assessment:	Dose-Response Assessment for Any Toxic Endpoint
Section(s):	4.1, 4.4
References:	New Procedure
Data Requirements:	Method requires both toxicity and exposure data on the mixture's components. Toxicity data are missing for some components.
Strategy of Method:	Scale component exposure concentrations relative to potency of an index chemical (typically the best-studied component) following expert committee consensus. Add scaled concentrations. Use dose-response curve of index chemical to generate response estimate for sum of scaled concentrations.
Ease of Use:	Complicated to use. Requires some statistical modeling and judgment of relative potency factors.
Assumptions:	Based on dose addition which carries with it assumptions of same mode of action and similarly shaped dose-response curves across the components. The "common mode-of-action" assumption can be met using a surrogate of toxicologic similarity, but for specific conditions (endpoint, route, duration).
Limitations:	Limited by data quality and similarity. May not have data from all routes of exposure of interest. Same mode-of-action across components may not be known.
Uncertainties:	Judgment of relative potency factors. Similarity of toxicologic action. Missing data on some components.

2.6.2. Independence and Response Addition

Response addition may apply when components act on different systems or produce effects that do not influence each other. Under response addition, the chemicals in the mixture are assumed to behave independently of one another, so that the body's response to the first chemical is the same whether or not the second chemical is present. Mathematically, response addition can be described by the statistical law of independent events, with "response" measured by the percentage of exposed animals that show toxicity or the proportion of the population responding. Response addition is particularly useful when the effects of concern are thought to be present at low dose levels for each of the component chemicals, even though it is highly unlikely the effects are capable of being observed at these low levels in the environment. When interaction data are available on any of the components in the mixture, the risk assessor may provide a qualitative discussion of the likely effect of these data on the outcome of the mixture risk assessment under response addition (see Sections 2.2.4, 4.5.4).

2.6.2.1. User Fact Sheet: Response Addition

The user of this guidance document can follow Figure 2-1 to determine that the data available are on the components of the mixture of concern and that there is evidence of toxicologic independence of action. Then a procedure is suggested for estimating risk from exposure to the mixture by using Response Addition, as encapsulated in the following user information fact sheet.

Approach:	Response Addition
Type of Assessment:	Risk Characterization for Any Toxic Endpoint
Section(s):	4.1, 4.5
References:	Used extensively for cancer. Used in Superfund site assessments (U.S. EPA, 1989a).
Data Requirements:	Method requires both toxicity data (measured in percent responding) and exposure data on the mixture's components. Good dose-response data are needed, such as what is available on IRIS (U.S. EPA, 2000a).
Strategy of Method:	Risk of an effect is estimated for each component using its dose-response curve at the component's exposure concentration. Component risks are added, using the independence formula, to yield a risk estimate for the total mixture for the specific exposure.
Ease of Use:	Easy to calculate.
Assumptions:	Assumes toxicologic independence of action. Assumes interactions are not significant at low exposures.
Limitations:	Limited to low exposure concentrations. Slight overestimate of mixture's upper bound on risk when adding individual component upper bound estimates. Restricted to independence of action.
Uncertainties:	Independence of action. Accuracy of exposure data. Individual risk estimates may vary in quality.

2.6.3. Interactions Data

Toxicologic interactions are operationally defined by the existence of data showing significant deviations from a "no interaction" prediction; that is, the response is different from what would be expected under an assumption of additivity (e.g., dose-additive, response-additive). Types of interactions among mixture components that can affect toxicologic response to the whole mixture include chemical-to-chemical, toxicokinetic, and toxicodynamic interactions (see Table B-2 and Appendix C). The impact of these constituent interactions on toxicologic response can be less than additive (e.g., antagonistic) or greater than additive (e.g., synergistic). The component-based method discussed in this document that incorporates interactions information is the interaction-based HI.

2.6.3.1. User Fact Sheet: Interaction-Based Hazard Index

The user of this guidance document can follow Figure 2-1 to determine that the data available are on the components of the mixture of concern and that interactions data are available. Then a procedure is suggested for estimating risk from exposure to the mixture by incorporating information on binary combinations of the components using an interaction-based hazard index, as encapsulated in the following user information fact sheet.

Approach:	Interaction-Based Hazard Index
Type of Assessment:	Risk Characterization for Any Toxic Endpoint
Section(s):	4.1, 4.3
References:	New procedure (Hertzberg et al., 1999).
Data Requirements:	Method requires both toxicity and exposure data on the mixture's components, and interactions data on at least one pair of components.
Strategy of Method:	Scale component exposure concentrations by a measure of relative potency (typically, divide by a reference dose/concentration [RfD/C]) for components with a similar mechanism-of-action. Modify this term with data on binary interactions. Add scaled/modified concentrations to provide an indicator of risk from exposure to the mixture of concern.
Ease of Use:	Complicated to use.
Assumptions:	Assumes binary interactions are the most important. Assumes interaction magnitude is not dose dependent, but depends on component proportions.
Limitations:	Limited interactions data are available. Model with relative proportions is untested. Interaction magnitude is often a default because of lack of measurement data.
Uncertainties:	Binary interactions used to represent the interactions for the whole mixture. Accuracy of exposure data. Accuracy of default for interaction magnitude.

2.7. FUTURE DIRECTIONS**2.7.1. Overview**

Risk assessment methods for chemical mixtures are progressing along paths similar to risk assessment for single chemicals, by incorporating more knowledge of specific modes of toxicologic action of the chemicals and by greater use of statistical methods and mathematical models. Where the field differs, however, is in the more extensive use of quantitative inference from tested chemicals to untested chemicals. Mixture exposures can be extremely varied, with differences in total dose, composition, and relative proportions. Consequently, only a small fraction of environmental mixtures can actually be tested for dose-response characteristics. Two options then seem feasible: directly investigating a few high-priority mixtures, and, for the remainder, developing extrapolation methods for using available data on the mixture components or on similar mixtures.

The first option requires priority setting, which for mixtures is its own research area (Cassee et al., 1998). The characteristics to include in a mixture prioritization scheme should parallel those often cited for single chemicals: target

those mixtures posing the highest public health risk. The supporting data could include annual emissions of mixtures, frequency of occurrence of mixtures in the environment, identity of mixtures containing highly toxic chemicals, or documented health problems in populations exposed to identified mixtures. Because most interaction data are on chemical pairs, one approach would include the frequency of occurrence of chemical pairs in the media associated with the exposure scenario to be regulated. The prioritization should also consider the availability of interaction data. For high-priority mixtures lacking such data, other assessment methods may be needed. The various regulatory program areas, such as Superfund waste sites, ambient air, and drinking water, pose substantially different kinds of mixtures and exposure conditions, so that a priority list for one program may not be appropriate for a different regulatory program.

Once a few mixtures posing the highest concern have been identified, researchers should seek to evaluate their exposure, toxicity, and risk characteristics. Because even the highest priority mixtures are likely to pose complex and varied exposure possibilities, much of the research effort should involve developing highly efficient experimental designs, short-term toxicity assays, and uncertainty methods so that several scenarios can be characterized for each mixture.

The second option, for addressing all the remaining mixtures, is to develop methods that can extrapolate exposure and toxicity estimates from available data to the scenario of concern. In addition to the issues being addressed by extrapolation methods for single chemicals (e.g., cross-species, cross-route), mixtures issues also include interactions and changes in composition. Interactions issues include the commonly observed toxicologic interactions that influence pharmacokinetics, as well as the less-studied areas of physiological interactions between affected tissues or organs, and the biochemical and physical interactions affecting degradation and transport of mixtures in environmental media. Because of the wide variety of mixture exposures, all relevant information should be tapped to improve the understanding of the basic biological and chemical processes. For example, to improve dose-response extrapolation, toxicology experiments, epidemiology and occupational studies, and mathematical model development should be pursued simultaneously.

Mixtures research should be efficient. The complexity of the issues is beyond the reach of any single agency. Sharing of resources and information within different sectors of EPA as well as with other agencies is essential. Several such efforts are underway. The Integral Search System (Arcos et al., 1988) and the Mixtox database (Marnicio et al., 1991) are two EPA collections of bibliographic summaries of interaction studies that are available to the public. Additional databases should be developed, perhaps jointly with the public, on mechanisms and modes of toxicologic interaction and on mathematical models of biological processes influencing

the interactions. The National Institute for Occupational Safety and Health (NIOSH) has a Mixed Exposures research program whose advisory committee includes representatives from EPA, other federal agencies, and research institutions. EPA, NIOSH, and the Agency for Toxic Substances Disease Registry (ATSDR) have organized the Mixed Exposures Research Group (MERG), composed of almost 20 federal and state agencies, to share regulatory approaches. MERG seeks to facilitate interagency communication and jointly sponsored research projects on mixtures. Additional cooperative efforts should be pursued with the public and foreign agencies.

Mixture risk assessment methods should ideally be developed in conjunction with those laboratory and field studies that are needed for implementation as well as validation. Otherwise, the methods become conceptual models that cannot feasibly be applied, or decision tools whose accuracy cannot be tested. One example concerns interaction studies, such as those detailed in the EPA's Mixtox database (Marnicio et al., 1991; U.S. EPA, 1990) of in vivo toxicologic interaction studies. In the Mixtox database, 95% of the studies involve only pairs of chemicals (Teuschler and Hertzberg, 1995). Consequently, the interaction-based Hazard Index (Section 4.3) was developed for pairwise interactions to allow use of available data. Interaction studies are in progress by research groups in EPA's National Center for Environmental Assessment (NCEA) and National Health and Environmental Effects Research Laboratory (NHEERL) to provide the toxicity data and data analysis methods for validation of the index.

The information required for evaluation of the extrapolation methods in this document is generally not yet available. The number of pairs studied for interactions is a small fraction of the number of possible chemical combinations, and the number of whole mixtures studied is far smaller yet. For example, with a simple mixture of only 20 chemicals, there are 190 pairs, but over a million possible combinations (pairs, triples, etc.). Because of this sparseness of existing data, both on whole mixtures and on interactions, the accuracy of these extrapolation methods will be difficult to judge. The inferential procedures for mixture risk discussed in this document are then likely to be adopted based on scientific plausibility and on relatively few validation studies. The validation process is valuable, even when incomplete. As was found with the analysis of the consistency of pairwise interactions (Durkin et al., 1995), the evaluation of the mixture risk tools will likely spawn research questions that lead to new statistical, exposure, and toxicologic studies, and subsequently to better risk tools.

2.7.2. Research Suggestions for Improving Mixture Risk Assessment

Several research directions have been suggested during the development of this guidance document. Although specific projects have been identified related to dose-response assessment, the highest priority was the preparation of guidance on exposure assessment of mixtures. Some of the key concerns with exposure assessment are discussed in this document (Section 2.4). The

need is for specific procedures for measurement and modeling of exposures for various scenarios, along with the corresponding methods for characterizing the uncertainties. The Risk Assessment Forum created an advisory panel in 1999 to decide the scope and project requirements for a framework for cumulative risk assessment. A major component of that framework is the exposure assessment of mixtures. Some specific areas for exposure assessment that have been suggested during review of this guidance are given in the list below.

Among the next highest priorities was research aimed at the evaluation and improvement of the dose-response methods in this guidance document. In particular, the comparative potency method for whole mixtures and the interaction-based Hazard Index need to be demonstrated with different kinds of mixtures. Methods for validation of these two methods also need to be developed, followed by the validation exercise itself for several different mixtures.

The most often mentioned research area was uncertainty analysis. Each of the methods in this guidance document produces a single risk estimate. An initial goal is to present that risk estimate as a plausible range in addition to the single recommended value. A related goal is to present a range of risk estimates that reflects all the risk methods applied to the mixture of concern, i.e., the uncertainty in model selection. Data uncertainties should also be addressed, at least by sensitivity analysis. Subsequent efforts should pursue more complete uncertainty characterization, including methods for choosing the default distributions for the parameters and variables in each method. Uncertainty characterization is also one of the components of the Forum's cumulative risk framework project, so further work will commence in this area over the next few years.

The other main research needs raised during the authoring and review of this guidance document covered a wide range of scientific areas. The most commonly discussed topics are in the following list. The research areas are roughly grouped by scientific discipline or application.

Exposure assessment

- data and models for degradation over several years (e.g., pathogens in groundwater, pesticide mixtures in soil).
- models/data for chemical and biological interactions influencing mixture transport.
- mixture changes (chemical composition, relative proportions) from facility failures (e.g., drinking water, municipal combustors).
- procedures for artificial degradation or weathering of complex mixtures.
- procedures for monitoring mixtures when there are hot spots with each spot having a different driver chemical.
- biomarkers of exposure that are specific to single chemicals or chemical classes and mathematical models that relate the biomarker to existing or prior external exposure levels, and to tissue levels and/or tissue-specific toxic effects.

Statistical/mathematical methods

- formulas for incorporating independence when adding upper-bound risks ($n > 3$).
- concepts and methods for tolerance distributions for $n > 2$ chemicals.
- uncertainty analysis, i.e., Bayesian, Monte Carlo simulation for each of the mixture risk assessment procedures.
- efficient and stable numerical methods for modeling highly complex interacting systems (hundreds of chemicals, multiple tissues, time-variable exposures).
- statistical graphics methods for demonstrating and displaying interactions in multichemical mixtures ($n > 5$).

Biomathematical models

- models for describing the dependence of interaction magnitude on total dose and on component fractions.
- biologically based models that separate out the relative differences of chemicals in terms of pharmacokinetics and pharmacodynamics.
- models that incorporate aging and growth, and more physiological processes and factors than just flows to major organs and tissues.
- models for initiation-promotion interactions that include background exposures to initiators or promoters.

Human studies

- database of epidemiology studies with exposure-response information on mixtures.
- database of occupational health studies with exposure-response information on mixtures.
- methods for estimating interaction magnitudes in epidemiology studies that relate to (are consistent with) physiologic measures of interaction magnitude.
- information on background exposure levels, background prevalence of health conditions, and those population characteristics that indicate increased susceptibility to toxic chemicals, including models that quantify the influence of population characteristics on toxicology.

Toxicology

- modes and mechanisms of interaction for carcinogens.
- data describing the dependence of interaction magnitude on total mixture dose and on component fractions.
- concordance across animal species of specific toxic effects, modes of action, and modes of interaction.
- data and modes of interaction for inhibition (one chemical is nontoxic).
- data and concepts for particulate interactions with other airborne chemicals.

- more examples and methods for short-term whole-mixture toxicity testing, particularly data showing the representativeness of in vitro studies to represent in vivo toxicity.
- relationships between mode of toxic action and mode of interaction.
- concepts, mechanisms or modes of action, or toxicity data to explain the mathematical interaction models of proportional response addition and straight-line isoboles that are not parallel.
- interaction studies on major chemical classes to establish empirical interaction classes based on interaction patterns.
- test procedures that mimic real-world exposures (e.g., species-adjusted intermittent exposures to correspond to occupational exposure patterns)
- biomarkers of toxicity that are specific to single (or related) toxic effects and mathematical models that relate the biomarker to actual measurable toxic endpoints.

Risk methods

- development of screening assays for mixtures to identify combinations of chemicals that are most toxic or that potentially interact.
- risk estimation for a mixture of mixed types, including similar, independent, and interacting chemicals with same target organ, e.g., for classes with similar (RPF) chemicals and other chemicals.
- risk estimates or qualitative risk indicators for unidentified chemicals in a mixture (see U.S. EPA, 1998d. Comparative risk framework methodology and case study. SAB external review draft. NCEA-C-0135).
- MOE methods for carcinogens using response addition.
- RPFs from dose-response data on all chemicals, as improvement over HI because it allows actual estimate of toxicity from the index chemical's dose-response curve.
- use of interaction patterns for estimating interaction direction in a chemical class.
- methods for prioritizing chemical pairs (air, drinking water) for further study on the basis of health risk.
- methods for prioritizing complex mixtures for further study on the basis of health risk.
- methods for prioritizing complex mixtures for further study on the basis of degradation potential.

EPA/630/R-98/002
September 1986

APPENDIX A

**Guidelines for the
Health Risk Assessment of
Chemical Mixtures**

Published on September 24, 1986, Federal Register 51(185):34014-34025

Risk Assessment Forum
U.S. Environmental Protection Agency
Washington, DC

DISCLAIMER

This document has been reviewed in accordance with U.S. Environmental Protection Agency policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

Note: This document represents the final guidelines. A number of editorial corrections have been made during conversion and subsequent proofreading to ensure the accuracy of this publication.

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GUIDELINES FOR THE HEALTH RISK ASSESSMENT OF CHEMICAL MIXTURES
[FRL-2984-2]

AGENCY: U.S. Environmental Protection Agency (EPA).

ACTION: Final Guidelines for the Health Risk Assessment of Chemical Mixtures.

SUMMARY: The U.S. Environmental Protection Agency is today issuing five guidelines for assessing the health risks of environmental pollutants. These are:

Guidelines for Carcinogen Risk Assessment

Guidelines for Estimating Exposures

Guidelines for Mutagenicity Risk Assessment

Guidelines for the Health Assessment of Suspect Developmental Toxicants

Guidelines for the Health Risk Assessment of Chemical Mixtures

This notice contains the Guidelines for the Health Risk Assessment of Chemical Mixtures; the other guidelines appear elsewhere in today's Federal Register.

The Guidelines for the Health Risk Assessment of Chemical Mixtures (hereafter "Guidelines") are intended to guide Agency analysis of information relating to health effects data on chemical mixtures in line with the policies and procedures established in the statutes administered by the EPA. These Guidelines were developed as part of an interoffice guidelines development program under the auspices of the Office of Health and Environmental Assessment (OHEA) in the Agency's Office of Research and Development. They reflect Agency consideration of public and Science Advisory Board (SAB) comments on the Proposed Guidelines for the Health Risk Assessment of Chemical Mixtures published January 9, 1985 (50 FR 1170).

This publication completes the first round of risk assessment guidelines development. These Guidelines will be revised, and new guidelines will be developed, as appropriate.

EFFECTIVE DATE: The Guidelines will be effective September 24, 1986.

FOR FURTHER INFORMATION CONTACT: Dr. Richard Hertzberg, Waste Management Division, U.S. Environmental Protection Agency, Atlanta Federal Center, 100 Alabama St., SW, Atlanta, GA 30303-3104, TEL: 404-562-8663.

SUPPLEMENTARY INFORMATION: In 1983, the National Academy of Sciences (NAS) published its book entitled *Risk Assessment in the Federal Government: Managing the Process*. In that book, the NAS recommended that Federal regulatory agencies establish “inference guidelines” to ensure consistency and technical quality in risk assessments and to ensure that the risk assessment process was maintained as a scientific effort separate from risk management. A task force within EPA accepted that recommendation and requested that Agency scientists begin to develop such guidelines.

General

The guidelines published today are products of a two-year Agencywide effort, which has included many scientists from the larger scientific community. These guidelines set forth principles and procedures to guide EPA scientists in the conduct of Agency risk assessments, and to inform Agency decision makers and the public about these procedures. In particular, the guidelines emphasize that risk assessments will be conducted on a case-by-case basis, giving full consideration to all relevant scientific information. This case-by-case approach means that Agency experts review the scientific information on each agent and use the most scientifically appropriate interpretation to assess risk. The guidelines also stress that this information will be fully presented in Agency risk assessment documents, and that Agency scientists will identify the strengths and weaknesses of each assessment by describing uncertainties, assumptions, and limitations, as well as the scientific basis and rationale for each assessment.

Finally, the guidelines are formulated in part to bridge gaps in risk assessment methodology and data. By identifying these gaps and the importance of the missing information to the risk assessment process, EPA wishes to encourage research and analysis that will lead to new risk assessment methods and data.

Guidelines for Health Risk Assessment of Chemical Mixtures

Work on the Guidelines for the Health Risk Assessment of Chemical Mixtures began in January 1984. Draft guidelines were developed by Agency work groups composed of expert scientists from throughout the Agency. The drafts were peer-reviewed by expert scientists in the fields of toxicology, pharmacokinetics, and statistics from universities, environmental groups, industry, labor, and other governmental agencies. They were then proposed for public comment in the Federal Register (50 FR 1170). On November 9, 1984, the Administrator directed that Agency offices use the proposed guidelines in performing risk assessments until final guidelines became available.

After the close of the public comment period, Agency staff prepared summaries of the comments, analyses of the major issues presented by the commentators, and preliminary Agency

responses to those comments. These analyses were presented to review panels of the SAB on March 4 and April 22-23, 1985, and to the Executive Committee of the SAB on April 25-26, 1985. The SAB meetings were announced in the Federal Register as follows: February 12, 1985 (50 FR 5811), and April 4, 1985 (50 FR 13420 and 13421).

In a letter to the Administrator dated June 19, 1985, the Executive Committee generally concurred on all five of the guidelines, but recommended certain revisions and requested that any revised guidelines be submitted to the appropriate SAB review panel chairman for review and concurrence on behalf of the Executive Committee. As described in the responses to comments (see Part B: Response to the Public and Science Advisory Board Comments), each guidelines document was revised, where appropriate, consistent with the SAB recommendations, and revised draft guidelines were submitted to the panel chairmen. Revised draft Guidelines for the Health Risk Assessment of Chemical Mixtures were concurred on in a letter dated August 16, 1985. Copies of the letters are available at the Public Information Reference Unit, EPA Headquarters Library, as indicated elsewhere in this notice.

Following this Preamble are two parts: Part A contains the Guidelines and Part B the Response to the Public and Science Advisory Board Comments (a summary of the major public comments, SAB comments, and Agency responses to those comments).

The SAB requested that the Agency develop a technical support document for these Guidelines. The SAB identified the need for this type of document due to the limited knowledge on interactions of chemicals in biological systems. Because of this, the SAB commented that progress in improving risk assessment will be particularly dependent upon progress in the science of interactions.

Agency staff have begun preliminary work on the technical support document and expect it to be completed by early 1987. The Agency is continuing to study the risk assessment issues raised in the guidelines and will revise these Guidelines in line with new information as appropriate.

References, supporting documents, and comments received on the proposed guidelines, as well as copies of the final guidelines, are available for inspection and copying at the Public Information Reference Unit (202-382-5926), EPA Headquarters Library, 401 M Street, SW, Washington, DC, between the hours of 8:00 a.m. and 4:30 p.m.

I certify that these Guidelines are not major rules as defined by Executive Order 12291, because they are nonbinding policy statements and have no direct effect on the regulated

community. Therefore, they will have no effect on costs or prices, and they will have no other significant adverse effects on the economy. These Guidelines were reviewed by the Office of Management and Budget under Executive Order 12291.

Dated: August 22, 1986

Signed by EPA Administrator
Lee M. Thomas

PART A: GUIDELINES FOR THE HEALTH RISK ASSESSMENT OF CHEMICAL MIXTURES

1. INTRODUCTION

The primary purpose of this document is to generate a consistent Agency approach for evaluating data on the chronic and subchronic effects of chemical mixtures. It is a procedural guide that emphasizes broad underlying principles of the various science disciplines (toxicology, pharmacology, statistics) necessary for assessing health risk from chemical mixture exposure. Approaches to be used with respect to the analysis and evaluation of the various data are also discussed.

It is not the intent of these Guidelines to regulate any social or economic aspects concerning risk of injury to human health or the environment caused by exposure to a chemical agent(s). All such action is addressed in specific statutes and federal legislation and is independent of these Guidelines.

While some potential environmental hazards involve significant exposure to only a single compound, most instances of environmental contamination involve concurrent or sequential exposures to a mixture of compounds that may induce similar or dissimilar effects over exposure periods ranging from short-term to lifetime. For the purposes of these Guidelines, mixtures will be defined as any combination of two or more chemical substances regardless of source or of spatial or temporal proximity. In some instances, the mixtures are highly complex, consisting of scores of compounds that are generated simultaneously as byproducts from a single source or process (e.g., coke oven emissions and diesel exhaust). In other cases, complex mixtures of related compounds are produced as commercial products (e.g., PCBs, gasoline and pesticide formulations) and eventually released to the environment. Another class of mixtures consists of compounds, often unrelated chemically or commercially, which are placed in the same area for disposal or storage, eventually come into contact with each other, and are released as a mixture to the environment. The quality and quantity of pertinent information available for risk assessment varies considerably for different mixtures. Occasionally, the chemical composition of a mixture is well characterized, levels of exposure to the population are known, and detailed toxicologic data on the mixture are available. Most frequently, not all components of the mixture are known, exposure data are uncertain, and toxicologic data on the known components of the mixture are limited. Nonetheless, the Agency may be required to take action because of the number of individuals at potential risk or because of the known toxicologic effects of these compounds that have been identified in the mixture.

The prediction of how specific mixtures of toxicants will interact must be based on an understanding of the mechanisms of such interactions. Most reviews and texts that discuss toxicant interactions attempt to discuss the biological or chemical bases of the interactions (e.g., Klaassen and Doull, 1980; Levine, 1973; Goldstein et al., 1974; NRC, 1980a; Veldstra, 1956; Withey, 1981). Although different authors use somewhat different classification schemes when discussing the ways in which toxicants interact, it generally is recognized that toxicant interactions may occur during any of the toxicologic processes that take place with a single compound: absorption, distribution, metabolism, excretion, and activity at the receptor site(s). Compounds may interact chemically, yielding a new toxic component or causing a change in the biological availability of the existing component. They may also interact by causing different effects at different receptor sites.

Because of the uncertainties inherent in predicting the magnitude and nature of toxicant interactions, the assessment of health risk from chemical mixtures must include a thorough discussion of all assumptions. No single approach is recommended in these Guidelines. Instead, guidance is given for the use of several approaches depending on the nature and quality of the data. Additional mathematical details are presented in Section 4.

In addition to these Guidelines, a supplemental technical support document is being developed which will contain a thorough review of all available information on the toxicity of chemical mixtures and a discussion of research needs.

2. PROPOSED APPROACH

No single approach can be recommended to risk assessments for multiple chemical exposures. Nonetheless, general guidelines can be recommended depending on the type of mixture, the known toxic effects of its components, the availability of toxicity data on the mixture or similar mixtures, the known or anticipated interactions among components of the mixture, and the quality of the exposure data. Given the complexity of this issue and the relative paucity of empirical data from which sound generalizations can be constructed, emphasis must be placed on flexibility, judgment, and a clear articulation of the assumptions and limitations in any risk assessment that is developed. The proposed approach is summarized in Table 1 and Figure 1 and is detailed below. An alphanumeric scheme for ranking the quality of the data used in the risk assessment is given in Table 2.

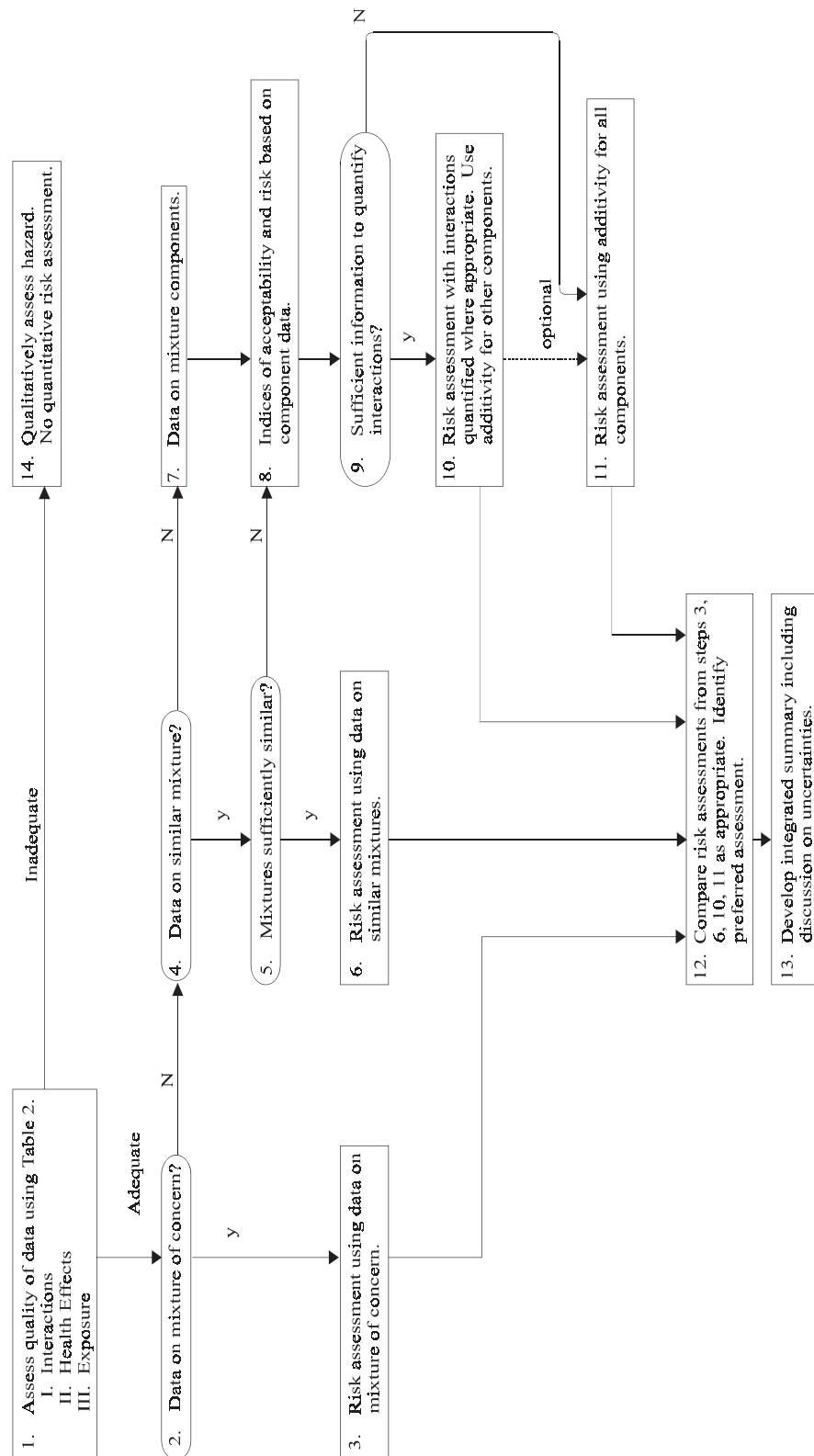
2.1. DATA AVAILABLE ON THE MIXTURE OF CONCERN

For predicting the effects of subchronic or chronic exposure to mixtures, the preferred approach usually will be to use subchronic or chronic health effects data on the mixture of

Table 1. Risk assessment approach for chemical mixtures

1. Assess the quality of the data on interactions, health effects, and exposure (see Table 2).
 - a. If adequate, proceed to Step 2.
 - b. If inadequate, proceed to Step 14.
2. Health effects information is available on the chemical mixture of concern.
 - a. If yes, proceed to Step 3.
 - b. If no, proceed to Step 4.
3. Conduct risk assessment on the mixture of concern based on health effects data on the mixture. Use the same procedures as those for single compounds. Proceed to Step 7 (optional) and Step 12.
4. Health effects information is available on a mixture that is similar to the mixture of concern.
 - a. If yes, proceed to Step 5.
 - b. If no, proceed to Step 7.
5. Assess the similarity of the mixture on which health effects data are available to the mixture of concern, with emphasis on any differences in components or proportions of components, as well as the effects that such differences would have on biological activity.
 - a. If sufficiently similar, proceed to Step 6.
 - b. If not sufficiently similar, proceed to Step 7.
6. Conduct risk assessment on the mixture of concern based on health effects data on the similar mixture. Use the same procedures as those for single compounds. Proceed to Step 7 (optional) and Step 12.
7. Compile health effects and exposure information on the components of the mixture.
8. Derive appropriate indices of acceptable exposure and/or risk on the individual components in the mixture. Proceed to Step 9.
9. Assess data on interactions of components in the mixtures.
 - a. If sufficient quantitative data are available on the interactions of two or more components in the mixture, proceed to Step 10.
 - b. If sufficient quantitative data are not available, use whatever information is available to qualitatively indicate the nature of potential interactions. Proceed to Step 11.
10. Use an appropriate interaction model to combine risk assessments on compounds for which data are adequate, and use an additivity assumption for the remaining compounds. Proceed to Step 11 (optional) and Step 12.
11. Develop a risk assessment based on an additivity approach for all compounds in the mixture. Proceed to Step 12.
12. Compare risk assessments conducted in Steps 5, 8, and 9. Identify and justify the preferred assessment, and quantify uncertainty, if possible. Proceed to Step 13.
13. Develop an integrated summary of the qualitative and quantitative assessments with special emphasis on uncertainties and assumptions. Classify the overall quality of the risk assessment, as indicated in Table 2. Stop.
14. No risk assessment can be conducted because of inadequate data on interactions, health effects, or exposure. Qualitatively assess the nature of any potential hazard and detail the types of additional data necessary to support a risk assessment. Stop.

Note—Several decisions used here, especially those concerning adequacy of data and similarity between two mixtures, are not precisely characterized and will require considerable judgment. See text.



A-4

Figure 1. Flow chart of the risk assessment in Table 1. Note that it may be desirable to conduct all three assessments when possible (i.e., using data on the mixture, a similar mixture, or the components) in order to make the fullest use of the available data. See text for further discussion.

Table 2. Classification scheme for the quality of the risk assessment of the mixture^a

Information on Interactions

- I. Assessment is based on data on the mixture of concern.
- II. Assessment is based on data on a sufficiently similar mixture.
- III. Quantitative interactions of components are well characterized.
- IV. The assumption of additivity is justified based on the nature of the health effects and on the number of component compounds.
- V. An assumption of additivity cannot be justified, and no quantitative risk assessment can be conducted.

Health Effects Information

- A. Full health effects data are available and relatively minor extrapolation is required.
- B. Full health effects data are available but extensive extrapolation is required for route or duration of exposure or for species differences. These extrapolations are supported by pharmacokinetic considerations, empirical observations, or other relevant information.
- C. Full health effects data are available, but extensive extrapolation is required for route or duration of exposure or for species differences. These extrapolations are not directly supported by the information available.
- D. Certain important health effects data are lacking and extensive extrapolations are required for route or duration of exposure or for species differences.
- E. A lack of health effects information on the mixture and its components in the mixture precludes a quantitative risk assessment.

Exposure Information^b

1. Monitoring information either alone or in combination with modeling information is sufficient to accurately characterize human exposure to the mixture or its components.
2. Modeling information is sufficient to reasonably characterize human exposure to the mixture or its components.
3. Exposure estimates for some components are lacking, uncertain, or variable. Information on health effects or environmental chemistry suggests that this limitation is not likely to substantially affect the risk assessment.
4. Not all components in the mixture have been identified, or levels of exposure are highly uncertain or variable. Information on health effects or environmental chemistry is not sufficient to assess the effect of this limitation on the risk assessment.
5. The available exposure information is insufficient for conducting a risk assessment.

^aSee text for discussion of sufficient similarity, adequacy of data, and justification for additivity assumptions.

^bSee the Agency's Guidelines for Estimating Exposures (U.S. EPA, 1986d) for more complete information on performing exposure assessments and evaluating the quality of exposure data.

concern and adopt procedures similar to those used for single compounds, either systemic toxicants or carcinogens (see U.S. EPA, 1986a-c). The risk assessor must recognize, however, that dose-response models used for single compounds are often based on biological mechanisms of the toxicity of single compounds, and may not be as well justified when applied to the mixture as a whole. Such data are most likely to be available on highly complex mixtures, such as coke oven emissions or diesel exhaust, which are generated in large quantities and associated with or suspected of causing adverse health effects. Attention should also be given to the persistence of the mixture in the environment as well as to the variability of the mixture composition over time or from different sources of emissions. If the components of the mixture are known to partition into different environmental compartments or to degrade or transform at different rates in the environment, then those factors must also be taken into account, or the confidence in and applicability of the risk assessment are diminished.

2.2. DATA AVAILABLE ON SIMILAR MIXTURES

If the risk assessment is based on data from a single mixture that is known to be generated with varying compositions depending on time or different emission sources, then the confidence in the applicability of the data to a risk assessment also is diminished. This can be offset to some degree if data are available on several mixtures of the same components that have different component ratios which encompass the temporal or spatial differences in composition of the mixture of concern. If such data are available, an attempt should be made to determine if significant and systematic differences exist among the chemical mixtures. If significant differences are noted, ranges of risk can be estimated based on the toxicologic data of the various mixtures. If no significant differences are noted, then a single risk assessment may be adequate, although the range of ratios of the components in the mixtures to which the risk assessment applies should also be given.

If no data are available on the mixtures of concern, but health effects data are available on a similar mixture (i.e., a mixture having the same components but in slightly different ratios, or having several common components but lacking one or more components, or having one or more additional components), a decision must be made whether the mixture on which health effects data are available is or is not “sufficiently similar” to the mixture of concern to permit a risk assessment. The determination of “sufficient similarity” must be made on a case-by-case basis, considering not only the uncertainties associated with using data on a dissimilar mixture but also the uncertainties of using other approaches such as additivity. In determining reasonable similarity, consideration should be given to any information on the components that differ or are contained in markedly different proportions between the mixture on which health effects data are available and the mixture of concern. Particular emphasis should be placed on any toxicologic or

pharmacokinetic data on the components or the mixtures which would be useful in assessing the significance of any chemical difference between the similar mixture and the mixtures of concern.

Even if a risk assessment can be made using data on the mixtures of concern or a reasonably similar mixture, it may be desirable to conduct a risk assessment based on toxicity data on the components in the mixture using the procedure outlined in Section 2.B. In the case of a mixture containing carcinogens and toxicants, an approach based on the mixture data alone may not be sufficiently protective in all cases. For example, this approach for a two-component mixture of one carcinogen and one toxicant would use toxicity data on the mixture of the two compounds. However, in a chronic study of such a mixture, the presence of the toxicant could mask the activity of the carcinogen. That is to say, at doses of the mixture sufficient to induce a carcinogenic effect, the toxicant could induce mortality so that at the maximum tolerated dose of the mixture, no carcinogenic effect could be observed. Since carcinogenicity is considered by the Agency to be a nonthreshold effect, it may not be prudent to construe the negative results of such a bioassay as indicating the absence of risk at lower doses. Consequently, the mixture approach should be modified to allow the risk assessor to evaluate the potential for masking, of one effect by another, on a case-by-case basis.

2.3. DATA AVAILABLE ONLY ON MIXTURE COMPONENTS

If data are not available on an identical or reasonably similar mixture, the risk assessment may be based on the toxic or carcinogenic properties of the components in the mixture. When little or no quantitative information is available on the potential interaction among the components, additive models (defined in the next section) are recommended for systemic toxicants. Several studies have demonstrated that dose additive models often predict reasonably well the toxicities of mixtures composed of a substantial variety of both similar and dissimilar compounds (Pozzani et al., 1959; Smyth et al., 1969, 1970; Murphy, 1980). The problem of multiple toxicant exposure has been addressed by the American Conference of Governmental Industrial Hygienists (ACGIH, 1983), the Occupational Safety and Health Administration (OSHA, 1983), the World Health Organization (WHO, 1981), and the National Research Council (NRC, 1980a,b). Although the focus and purpose of each group was somewhat different, all groups that recommended an approach elected to adopt some type of dose additive model. Nonetheless, as discussed in Section 4, dose additive models are not the most biologically plausible approach if the compounds do not have the same mode of toxicologic action. Consequently, depending on the nature of the risk assessment and the available information on modes of action and patterns of joint action, the Federal Register most reasonable additive model should be used.

2.3.1. Systemic Toxicants

For systemic toxicants, the current risk assessment methodology used by the Agency for single compounds most often results in the derivation of an exposure level which is not anticipated to cause significant adverse effects. Depending on the route of exposure, media of concern, and the legislative mandate guiding the risk assessments, these exposure levels may be expressed in a variety of ways such as acceptable daily intakes (ADIs) or reference doses (RfDs), levels associated with various margins of safety (MOS), or acceptable concentrations in various media. For the purpose of this discussion, the term “acceptable level” (AL) will be used to indicate any such criteria or advisories derived by the Agency. Levels of exposure (E) will be estimates obtained following the most current Agency Guidelines for Estimating Exposures (U.S. EPA, 1986d). For such estimates, the “hazard index” (HI) of a mixture based on the assumption of dose addition may be defined as:

$$HI = E_1/AL_1 + E_2/AL_2 + \dots + E_i/AL_i \quad (2-1)$$

where:

E_i = exposure level to the i^{th} toxicant* and AL_i = maximum acceptable level for the i^{th} toxicant.

Since the assumption of dose addition is most properly applied to compounds that induce the same effect by similar modes of action, a separate hazard index should be generated for each end point of concern. Dose addition for dissimilar effects does not have strong scientific support, and, if done, should be justified on a case-by-case basis in terms of biological plausibility.

The assumption of dose addition is most clearly justified when the mechanisms of action of the compounds under consideration are known to be the same. Since the mechanisms of action for most compounds are not well understood, the justification of the assumption of dose addition will often be limited to similarities in pharmacokinetic and toxicologic characteristics. In any event, if a hazard index is generated the quality of the experimental evidence supporting the assumption of dose addition must be clearly articulated.

The hazard index provides a rough measure of likely toxicity and requires cautious interpretation. The hazard index is only a numerical indication of the nearness to acceptable limits of exposure or the degree to which acceptable exposure levels are exceeded. As this index approaches unity, concern for the potential hazard of the mixture increases. If the index exceeds unity, the concern is the same as if an individual chemical exposure exceeded its acceptable level by the same proportion. The hazard index does not define dose-response relationships, and its numerical value should not be construed to be a direct estimate of risk. Nonetheless, if sufficient

data are available to derive individual acceptable levels for a spectrum of effects (e.g., MFO induction, minimal effects in several organs, reproductive effects, and behavioral effects), the hazard index may suggest what types of effects might be expected from the mixture exposure. If the components' variabilities of the acceptable levels are known, or if the acceptable levels are given as ranges (e.g., associated with different margins of safety), then the hazard index should be presented with corresponding estimates of variation or range.

Most studies on systemic toxicity report only descriptions of the effects in each dose group. If dose-response curves are estimated for systemic toxicants, however, dose-additive or response-additive assumptions can be used, with preference given to the most biologically plausible assumption (see Section 4 for the mathematical details).

2.3.2. Carcinogens

For carcinogens, whenever linearity of the individual dose-response curves has been assumed (usually restricted to low doses), the increase in risk P (also called excess or incremental risk), caused by exposure d , is related to carcinogenic potency B , as:

$$P = d B \quad (2-2)$$

For multiple compounds, this equation may be generalized to:

$$P = \sum d_i B_i \quad (2-3)$$

This equation assumes independence of action by the several carcinogens and is equivalent to the assumption of dose addition as well as to response addition with completely negative correlation of tolerance, as long as $P < 1$ (see Section 4). Analogous to the procedure used in Equation 2-1 for systemic toxicants, an index for n carcinogens can be developed by dividing exposure levels (E) by doses (DR) associated with a set level of risk:

$$HI = E_1/DR_1 + E_2/DR_2 + \dots + E_n/DR_n \quad (2-4)$$

Note that the less linear the dose-response curve is, the less appropriate Equations 2-3 and 2-4 will be, perhaps even at low doses. It should be emphasized that because of the uncertainties in estimating dose-response relationships for single compounds, and the additional uncertainties in combining the individual estimate to assess response from exposure to mixtures, response rates and hazard indices may have merit in comparing risks but should not be regarded as measures of absolute risk.

2.3.3. Interactions

None of the above equations incorporates any form of synergistic or antagonistic interaction. Some types of information, however, may be available that suggest that two or more components in the mixture may interact. Such information must be assessed in terms of both its relevance to subchronic or chronic hazard and its suitability for quantitatively altering the risk assessment.

For example, if chronic or subchronic toxicity or carcinogenicity studies have been conducted that permit a quantitative estimation of interaction for two chemicals, then it may be desirable to consider using equations detailed in Section 4, or modifications of these equations, to treat the two compounds as a single toxicant with greater or lesser potency than would be predicted from additivity. Other components of the mixture, on which no such interaction data are available, could then be separately treated in an additive manner. Before such a procedure is adopted, however, a discussion should be presented of the likelihood that other compounds in the mixture may interfere with the interaction of the two toxicants on which quantitative interaction data are available. If the weight of evidence suggests that interference is likely, then a quantitative alteration of the risk assessment may not be justified. In such cases, the risk assessment may only indicate the likely nature of interactions, either synergistic or antagonistic, and not quantify their magnitudes.

Other types of information, such as those relating to mechanisms of toxicant interaction, or quantitative estimates of interaction between two chemicals derived from acute studies, are even less likely to be of use in the quantitative assessment of long-term health risks. Usually it will be appropriate only to discuss these types of information, indicate the relevance of the information to subchronic or chronic exposure, and indicate, if possible, the nature of potential interactions, without attempting to quantify their magnitudes.

When the interactions are expected to have a minor influence on the mixture's toxicity, the assessment should indicate, when possible, the compounds most responsible for the predicted toxicity. This judgment should be based on predicted toxicity of each component, based on exposure and toxic or carcinogenic potential. This potential alone should not be used as an indicator of the chemicals posing the most hazard.

2.3.4. Uncertainties

For each risk assessment, the uncertainties should be clearly discussed and the overall quality of the risk assessment should be characterized. The scheme outlined in Table 2 should be used to express the degree of confidence in the quality of the data on interaction, health effects, and exposure.

- a. Health Effects—In some cases, when health effects data are incomplete, it may be possible to argue by analogy or quantitative structure-activity relationships that the compounds on which no health effects data are available are not likely to significantly affect the toxicity of the mixture. If a risk assessment includes such an argument, the limitations of the approach must be clearly articulated. Since a methodology has not been adopted for estimating an acceptable level (e.g., ADI) or carcinogenic potential for single compounds based either on quantitative structure-activity relationships or on the results of short-term screening tests, such methods are not at present recommended as the sole basis of a risk assessment on chemical mixtures.
- b. Exposure Uncertainties—The general uncertainties in exposure assessment have been addressed in the Agency's Guidelines for Estimating Exposures (U.S. EPA, 1986d). The risk assessor should discuss these exposure uncertainties in terms of the strength of the evidence used to quantify the exposure. When appropriate, the assessor should also compare monitoring and modeling data and discuss any inconsistencies as a source of uncertainty. For mixtures, these uncertainties may be increased as the number of compounds of concern increases.

If levels of exposure to certain compounds known to be in the mixture are not available, but information on health effects and environmental persistence and transport suggest that these compounds are not likely to be significant in affecting the toxicity of the mixture, then a risk assessment can be conducted based on the remaining compounds in the mixture, with appropriate caveats. If such an argument cannot be supported, no final risk assessment can be performed until adequate monitoring data are available. As an interim procedure, a risk assessment may be conducted for those components in the mixture for which adequate exposure and health effects data are available. If the interim risk assessment does not suggest a hazard, there is still concern about the risk from such a mixture because not all components in the mixture have been considered.

- c. Uncertainties Regarding Composition of the Mixture—In perhaps a worst-case scenario, information may be lacking not only on health effects and levels of exposure, but also on the identity of some components of the mixture. Analogous to the procedure described in the previous paragraph, an interim risk assessment can be conducted on those components of the mixture for which adequate health effects and exposure information are available. If the risk is considered unacceptable, a conservative approach is to present the quantitative estimates of risk, along with appropriate qualifications regarding the incompleteness of the data. If no hazard is indicated by this partial assessment, the risk assessment should not be quantified until better health effects and monitoring data are available to adequately characterize the mixture exposure and potential hazards.

3. ASSUMPTIONS AND LIMITATIONS

3.1. INFORMATION ON INTERACTIONS

Most of the data available on toxicant interactions are derived from acute toxicity studies using experimental animals in which mixtures of two compounds were tested, often in only a single combination. Major areas of uncertainty with the use of such data involve the appropriateness of interaction data from an acute toxicity study for quantitatively altering a risk assessment for subchronic or chronic exposure, the appropriateness of interaction data on two component mixtures for quantitatively altering a risk assessment on a mixture of several compounds, and the accuracy of interaction data on experimental animals for quantitatively predicting interactions in humans.

The use of interaction data from acute toxicity studies to assess the potential interactions on chronic exposure is highly questionable unless the mechanisms of the interaction on acute exposure were known to apply to low-dose chronic exposure. Most known biological mechanisms for toxicant interactions, however, involve some form of competition between the chemicals or phenomena involving saturation of a receptor site or metabolic pathway. As the doses of the toxicants are decreased, it is likely that these mechanisms either no longer will exert a significant effect or will be decreased to an extent that cannot be measured or approximated.

The use of information from two-component mixtures to assess the interactions in a mixture containing more than two compounds also is questionable from a mechanistic perspective. For example, if two compounds are known to interact, either synergistically or antagonistically, because of the effects of one compound on the metabolism or excretion of the other, the addition of a third compound which either chemically alters or affects the absorption of one of the first two compounds could substantially alter the degree of the toxicologic interaction. Usually, detailed studies quantifying toxicant interactions are not available on multicomponent mixtures, and the few studies that are available on such mixtures (e.g., Gullino et al., 1956) do not provide sufficient information to assess the effects of interactive interference. Concerns with the use of interaction data on experimental mammals to assess interactions in humans is based on the increasing appreciation for systematic differences among species in their response to individual chemicals. If systematic differences in toxic sensitivity to single chemicals exist among species, then it seems reasonable to suggest that the magnitude of toxicant interactions among species also may vary in a systematic manner.

Consequently, even if excellent chronic data are available on the magnitude of toxicant interactions in a species of experimental mammal, there is uncertainty that the magnitude of the interaction will be the same in humans. Again, data are not available to properly assess the significance of this uncertainty.

Last, it should be emphasized that none of the models for toxicant interaction can predict the magnitude of toxicant interactions in the absence of extensive data. If sufficient data are available to estimate interaction coefficients as described in Section 4, then the magnitude of the toxicant interactions for various proportions of the same components can be predicted. The availability of an interaction ratio (observed response divided by predicted response) is useful only in assessing the magnitude of the toxicant interaction for the specific proportions of the mixture which was used to generate the interaction ratio.

The basic assumption in the recommended approach is that risk assessments on chemical mixtures are best conducted using toxicologic data on the mixture of concern or a reasonably similar mixture. While such risk assessments do not formally consider toxicologic interactions as part of a mathematical model, it is assumed that responses in experimental mammals or human populations noted after exposure to the chemical mixture can be used to conduct risk assessments on human populations. In bioassays of chemical mixtures using experimental mammals, the same limitations inherent in species-to-species extrapolation for single compounds apply to mixtures. When using health effects data on chemical mixtures from studies on exposed human populations, the limitations of epidemiologic studies in the risk assessment of single compounds also apply to mixtures. Additional limitations may be involved when using health effects data on chemical mixtures if the components in the mixture are not constant or if the components partition in the environment.

3.2. ADDITIVITY MODELS

If sufficient data are not available on the effects of the chemical mixture of concern or a reasonably similar mixture, the proposed approach is to assume additivity. Dose additivity is based on the assumption that the components in the mixture have the same mode of action and elicit the same effects. This assumption will not hold true in most cases, at least for mixtures of systemic toxicants. For systemic toxicants, however, most single compound risk assessments will result in the derivation of acceptable levels, which, as currently defined, cannot be adapted to the different forms of response additivity as described in Section 4.

Additivity models can be modified to incorporate quantitative data on toxicant interactions from subchronic or chronic studies using the models given in Section 4 or modifications of these models. If this approach is taken, however, it will be under the assumption that other components in the mixture do not interfere with the measured interaction. In practice, such subchronic or chronic interactions data seldom will be available. Consequently, most risk assessments (on mixtures) will be based on an assumption of additivity, as long as the components elicit similar effects.

Dose-additive and response-additive assumptions can lead to substantial errors in risk estimates if synergistic or antagonistic interactions occur. Although dose additivity has been shown to predict the acute toxicities of many mixtures of similar and dissimilar compounds (e.g., Pozzani et al., 1959; Smyth et al., 1969, 1970; Murphy, 1980), some marked exceptions have been noted. For example, Smyth et al. (1970) tested the interaction of 53 pairs of industrial chemicals based on acute lethality in rats. For most pairs of compounds, the ratio of the predicted LD_{50} to observed LD_{50} did not vary by more than a factor of 2. The greatest variation was seen with an equivolume mixture of morpholine and toluene, in which the observed LD_{50} was about five times less than the LD_{50} predicted by dose addition. In a study by Hammond et al. (1979), the relative risk of lung cancer attributable to smoking was 11, while the relative risk associated with asbestos exposure was 5. The relative risk of lung cancer from both smoking and asbestos exposure was 53, indicating a substantial synergistic effect. Consequently, in some cases, additivity assumptions may substantially underestimate risk. In other cases, risk may be overestimated. While this is certainly an unsatisfactory situation, the available data on mixtures are insufficient for estimating the magnitude of these errors. Based on current information, additivity assumptions are expected to yield generally neutral risk estimates (i.e., neither conservative nor lenient) and are plausible for component compounds that induce similar types of effects at the same sites of action.

4. MATHEMATICAL MODELS AND THE MEASUREMENT OF JOINT ACTION

The simplest mathematical models for joint action assume no interaction in any mathematical sense. They describe either dose addition or response addition and are motivated by data on acute lethal effects of mixtures of two compounds.

4.1. DOSE ADDITION

Dose addition assumes that the toxicants in a mixture behave as if they were dilutions or concentrations of each other, thus the true slopes of the dose-response curves for the individual compounds are identical, and the response elicited by the mixture can be predicted by summing the individual doses after adjusting for differences in potency; this is defined as the ratio of equitoxic doses. Probit transformation typically makes this ratio constant at all doses when parallel straight lines are obtained. Although this assumption can be applied to any model (e.g., the one-hit model in NRC, 1980b), it has been most often used in toxicology with the log-dose probit response model, which will be used to illustrate the assumption of dose addition. Suppose that two toxicants show the following log-dose probit response equations:

$$Y_1 = 0.3 + 3 \log Z_1 \quad (4-1)$$

$$Y_2 = 1.2 + 3 \log Z_2 \quad (4-2)$$

where Y_i is the probit response associated with a dose of Z_i ($i = 1, 2$). The potency, p , of toxicant #2 with respect to toxicant #1 is defined by the quantity Z_1/Z_2 when $Y_1 = Y_2$ (that is what is meant by equitoxic doses). In this example, the potency, p , is approximately 2. Dose addition assumes that the response, Y , to any mixture of these two toxicants can be predicted by

$$Y = 0.3 + 3 \log (Z_1 + pZ_2) \quad (4-3)$$

Thus, since p is defined as Z_1/Z_2 , Equation 4-3 essentially converts Z_2 into an equivalent dose of Z_1 by adjusting for the difference in potency. A more generalized form of this equation for any number of toxicants is:

$$Y = a_1 + b \log (f_1 + \sum f_i p_i) + b \log Z \quad (4-4)$$

where:

a_1 = the y-intercept of the dose-response equation for toxicant #1

b = the slope of the dose-response lines for the toxicants

f_i = the proportion of the i^{th} toxicant in the mixture

p_i = the potency of the i^{th} toxicant with respect to toxicant #1 (i.e., Z_1/Z_i); and

Z = the sum of the individual doses in the mixture.

A more detailed discussion of the derivation of the equations for dose addition is presented by Finney (1971).

4.2. RESPONSE ADDITION

The other form of additivity is referred to as response addition. As detailed by Bliss (1939), this type of joint action assumes that the two toxicants act on different receptor systems and that the correlation of individual tolerances may range from completely negative ($r = -1$) to completely positive ($r = +1$). Response addition assumes that the response to a given concentration of a mixture of toxicants is completely determined by the responses to the components and the pairwise correlation coefficient. Taking P as the proportion of organisms responding to a mixture of two toxicants which evoke individual responses of P_1 and P_2 , then.

$$P = P_1 \text{ if } r = 1 \text{ and } P_1 \geq P_2 \quad (4-5)$$

$$P = P_2 \text{ if } r = 1 \text{ and } P_1 < P_2 \quad (4-6)$$

$$P = P_1 + P_2 (1 - P_1) \text{ if } r = 0 \quad (4-7)$$

$$P = P_1 + P_2 \text{ if } r = -1 \text{ and } P \leq 1. \quad (4-8)$$

More generalized mathematical models for this form of joint action have been given by Plackett and Hewlett (1948).

4.3. INTERACTIONS

All of the above models assume no interactions and therefore do not incorporate measurements of synergistic or antagonistic effects. For measuring toxicant interactions for mixtures of two compounds, Finney (1942) proposed the following modification of Equation 4-4 for dose addition:

$$Y = a_1 + b \log (f_1 + pf_2 + K [pf_1f_2]^{0.5}) + b \log Z \quad (4-9)$$

where a_1 , b , f_1 , f_2 , p , and Z are defined as before, and K is the coefficient of interaction. A positive value of K indicates synergism, a negative value indicates antagonism, and a value of zero corresponds to dose addition as in Equation 4-4. Like other proposed modifications of dose addition (Hewlett, 1969), the equation assumes a consistent interaction throughout the entire range of proportions of individual components. To account for such asymmetric patterns of interaction as those observed by Alstott et al. (1973), Durkin (1981) proposed the following modification to Equation 4-9:

$$Y = a_1 + b \log (f_1 + pf_2 + K_1f_1 [pf_1f_2]^{0.5} + K_2f_2[pf_1f_2]^{0.5}) + b \log z \quad (4-10)$$

in which $K(pf_1f_2)^{0.5}$ is divided into two components, $K_1f_1 (pf_1f_2)^{0.5}$ and $K_2f_2[pf_1f_2]^{0.5}$. Since K_1 and K_2 need not have the same sign, apparent instances of antagonism at one receptor site and synergism at another receptor site can be estimated. When K_1 and K_2 are equal, Equation 4-10 reduces to Equation 4-9.

It should be noted that to obtain a reasonable number of degrees of freedom in the estimation of K in Equation 4-9 or K_1 and K_2 in Equation 4-10, the toxicity of several different combinations of the two components must be assayed along with assays of the toxicity of the individual components. Since this requires experiments with large numbers of animals, such analyses have been restricted for the most part to data from acute bioassays using insects (e.g., Finney, 1971) or aquatic organisms (Durkin, 1979). Also, because of the complexity of

experimental design and the need for large numbers of animals, neither Equation 4-9 nor Equation 4-10 has been generalized or applied to mixtures of more than two toxicants. Modifications of response-additive models to include interactive terms have also been proposed, along with appropriate statistical tests for the assumption of additivity (Korn and Liu, 1983; Wahrendorf et al., 1981).

In the epidemiologic literature, measurements of the extent of toxicant interactions, S , can be expressed as the ratio of observed relative risk to relative risk predicted by some form of additivity assumption. Analogous to the ratio of interaction in classical toxicology studies, $S = 1$ indicates no interaction, $S > 1$ indicates synergism, and $S < 1$ indicates antagonism. Several models for both additive and multiplicative risks have been proposed (e.g., Hogan et al., 1978; NRC, 1980b; Walter, 1976). For instance, Rothman (1976) has discussed the use of the following measurement of toxicant interaction based on the assumption of risk additivity:

$$S = (R_{11} - 1)/(R_{10} + R_{01} - 2) \quad (4-11)$$

where R_{10} is the relative risk from compound #1 in the absence of compound #2, R_{01} is the relative risk from compound #2 in the absence of compound #1, and R_{11} is the relative risk from exposure to both compounds. A multiplicative risk model adapted from Walter and Holford (1978, Equation 4) can be stated as:

$$S = R_{11}/(R_{10} R_{01}) \quad (4-12)$$

As discussed by both Walter and Holford (1978) and Rothman (1976), the risk-additive model is generally applied to agents causing diseases while the multiplicative model is more appropriate to agents that prevent disease. The relative merits of these and other indices have been the subject of considerable discussion in the epidemiologic literature (Hogan et al., 1978; Kupper and Hogan, 1978; Rothman, 1978; Rothman et al., 1980; Walter and Holford, 1978). There seems to be a consensus that for public health concerns regarding causative (toxic) agents, the additive model is more appropriate.

Both the additive and multiplicative models assume statistical independence in that the risk associated with exposure to both compounds in combination can be predicted by the risks associated with separate exposure to the individual compounds. As illustrated by Siemiatycki and Thomas (1981) for multistage carcinogenesis, the better fitting statistical model will depend not only upon actual biological interactions, but also upon the stages of the disease process which the compounds affect. Consequently, there is no a priori basis for selecting either type of model in a risk assessment. As discussed by Stara et al. (1983), the concepts of

multistage carcinogenesis and the effects of promoters and cocarcinogens on risk are extremely complex issues. Although risk models for promoters have been proposed (e.g., Bums et al., 1983), no single approach can be recommended at this time.

5. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 1983. TLVS: threshold limit values for chemical substances and physical agents in the work environment with intended changes for 1983-1984. Cincinnati, OH, p. 58.

Alatott, R.L, M.E. Tarrant, and R.B. Forney. 1973. The acute toxicities of 1-methylxanthine, ethanol, and 1-methylxanthine/ethanol combinations in the mouse. Toxicol. Appl. Pharmacol. 24:393-404.

Bliss, C.I. 1939. The toxicity of poisons applied jointly. Ann. Appl. Biol. 26:585-615.

Bums, F., R. Albert, F. Altschuler, and E. Morris. 1983. Approach to risk assessment for genotoxic carcinogens based on data from the mouse skin initiation-promotion model. Environ. Health Perspect. 50:309-320.

Durkin, P.R. 1979. Spent chlorination liquor and chlorophenolics: a study in detoxication and joint action using *Daphnia magna*. Ph.D. Thesis, Syracuse, NY: State University of New York College of Environmental Science and Forestry, p. 145.

Durkin, P.R. 1981. An approach to the analysis of toxicant interactions in the aquatic environment. Proceedings of the 4th Annual Symposium on Aquatic Toxicology. American Society for Testing and Materials, p. 388-401.

Finney, D.J. 1942. The analysis of toxicity tests on mixtures of poisons. Ann. Appl. Biol. 29:82-94.

Finney, D.J. 1971. Probit analysis. 3rd ed. Cambridge, Great Britain: Cambridge University Press, 333 p.

Goldstein, A., L. Aronow, and S.M. Kalman. 1974. Principles of drug action: the basis of pharmacology, 2nd ed. New York, NY: John Wiley and Sons, Inc., 854 p.

Gullino, P., M. Winitz, S.M. Birnbaum, J. Cornfield, M.C. Otey, and J.P. Greenstein. 1956. Studies on the metabolism of amino acids and related compounds *in vivo*. I. Toxicity of essential amino acids, individually and in mixtures, and the protective effect of L-arginine. Arch. Biochem. Biophys. 64:319-332.

Hammond, E.C., I.V. Selikoff, and H. Seidman. 1979. Asbestos exposure, cigarette smoking and death rates. Ann. NY Acad. Sci. 330:473-490.

Hewlett, P.S. 1969. Measurement of the potencies of drug mixtures. Biometrics 25:477-487.

Hogan, M.D., L. Kupper, B. Most, and J. Haseman. 1978. Alternative approaches to Rothman's approach for assessing synergism (or antagonism) in cohort studies. Am J. Epidemiol. 108(1):60-67.

Klaassen, C.D., and J. Doull. 1980. Evaluation of safety: toxicologic evaluation. In: J. Doull, C.D. Klaassen, and M.O. Amdur, eds. Toxicology: the basic science of poisons. New York, NY: Macmillan Publishing Co., Inc., p. 11-27.

Kom, E.L, and P-Y. Liu. 1963. Interactive effects of mixtures of stimuli in life table analysis. Biometrika 70:103-110.

Kupper, L., and M.D. Hogan. 1978. Interaction in epidemiologic studies. Am. J. Epidemiol. 108(6):447-453.

Levine, R.E. 1973. Pharmacology: drug actions and reactions. Boston, MA: Little, Brown and Company, 412 p.

Murphy, S.D. 1980. Assessment of the potential for toxic interactions among environmental pollutants. In: C.L. Galli, S.D. Murphy, and R. Paoletti, eds. The principles and methods in modern toxicology. Amsterdam, The Netherlands: Elsevier/North Holland Biomedical Press.

NRC (National Research Council). 1980a. Drinking water and health, Vol. 3. Washington, DC: National Academy Press, p. 27-28.

NRC (National Research Council). 1980b. Principles of toxicological interactions associated with multiple chemical exposures. Washington, DC: National Academy Press, p. 204.

OSHA (Occupational Safety and Health Administration). 1983. General Industry Standards, Subpart 2, Toxic and Hazardous Substances. Code of Federal Regulations. 40:1910.1000 (d)(2)(i). Chapter XVII—Occupational Safety and Health Administration, p. 667.

Plackett, R.L., and P.S. Hewlett. 1948. Statistical aspects of the independent joint action of poisons. *Ann. Appl. Biol.* 35:347-358.

Pozzani, U.C., C.S. Weil, and C.P. Carpenter. 1959. The toxicological basis of threshold values: 5. The experimental inhalation of vapor mixtures by rats, with notes upon the relationship between single dose inhalation and single dose oral data. *Am. Ind. Hyg. Assoc. J.* 20:364-369.

Rothman, K. 1976. The estimation of synergy or antagonism. *Am. J. Epidemiol.* 103(5):506-511.

Rothman, K. 1978. Estimation versus detection in the assessment of synergy. *Am. J. Epidemiol.* 108(1):9-11.

Rothman, K., S. Greenland, and A. Walker. 1980. Concepts of interaction. *Am. J. Epidemiol.* 112(4):467-470.

Siemiatycki, J., and D.C. Thomas. 1981. Biological models and statistical interactions: An example from multistage carcinogenesis. *Int. J. Epidemiol.* 10(4):383-387.

Smyth, H.F., C.S. Weil, I.S. West, and C.P. Carpenter. 1969. An exploration of joint toxic action: I. Twenty-seven industrial chemicals intubated in rats in all possible pairs. *Toxicol. Appl. Pharmacol.* 14:340-347.

Smyth, H.F., C.S. Weil, J.S. West, and C.P. Carpenter. 1970. An exploration of joint toxic action. II. Equitoxic versus equivolume mixtures. *Toxicol. Appl. Pharmacol.* 17:498-503.

Stara, J.F., D. Mukerjee, R. McGaughy, P. Durkin, and M.L. Dourson. 1983. The current use of studies on promoters and cocarcinogens in quantitative risk assessment. *Environ. Health Perspect.* 50:359-368.

U.S. EPA. 1986a. Guidelines for carcinogen risk assessment. Federal Register.

U.S. EPA. 1986b. Guidelines for mutagenicity risk assessment. Federal Register.

U.S. EPA. 1986c. Guidelines for the health assessment of developmental toxicants. Federal Register.

U.S. EPA. 1986d. Guidelines for estimating exposures. Federal Register.

Veldstra, H. 1956. Synergism and potentiation with special reference to the combination of structural analogues. *Pharmacol. Rev.* 8:339-387.

Wahrendorf, J., R. Zentgraf, and C.C. Brown. 1981. Optimal designs for the analysis of interactive effects of two carcinogens or other toxicants. *Biometrics* 37:45-54.

Walter, S.D. 1976. The estimation and interpretation of attributable risk in health research. *Biometrics* 32:829-849.

Walter, S.D., and T.R. Holford. 1978. Additive, multiplicative, and other models for disease risks. *Am. J. Epidemiol.* 108:341-346.

Withey, J.R. 1981. Toxicodynamics and biotransformation. In: *International Workshop on the Assessment of Multichemical Contamination*. Milan, Italy. (Draft copy courtesy of J.R. Withey).

WHO (World Health Organization). 1981. Health effects of combined exposures in the work environment. WHO Tech. Report Series No. 662.

PART B: RESPONSE TO PUBLIC AND SCIENCE ADVISORY BOARD COMMENTS

1. INTRODUCTION

This section summarizes some of the major issues raised in public comments on the Proposed Guidelines for the Health Risk Assessment of Chemical Mixtures published on January 9, 1985 (50 FR 1170). Comments were received from 14 individuals or organizations. An issue paper reflecting public and external review comments was presented to the Chemical Mixtures Guidelines Panel of the Science Advisory Board (SAB) on March 4, 1985. At its April 22-23, 1985, meeting, the SAB Panel provided the Agency with additional suggestions and recommendations concerning the Guidelines. This section also summarizes the issues raised by the SAB.

The SAB and public commentators expressed diverse opinions and addressed issues from a variety of perspectives. In response to comments, the Agency has modified or clarified many sections of the Guidelines, and is planning to develop a technical support document in line with the SAB recommendations. The discussion that follows highlights significant issues raised in the comments, and the Agency's response to them. Also, many minor recommendations, which do not warrant discussion here, were adopted by the Agency.

2. RECOMMENDED PROCEDURES

2.1. DEFINITIONS

Several comments were received concerning the lack of definitions for certain key items and the general understandability of certain sections. Definitions have been rewritten for several terms and the text has been significantly rewritten to clarify the Agency's intent and meaning.

Several commentators noted the lack of a precise definition of "mixture," even though several classes of mixtures are discussed. In the field of chemistry, the term "mixture" is usually differentiated from true solutions, with the former defined as nonhomogeneous multicomponent systems. For these Guidelines, the term "mixture" is defined as ". . . any combination of two or more chemicals regardless of spatial or temporal homogeneity of source" (Section 1). These Guidelines are intended to cover risk assessments for any situation where the population is exposed or potentially exposed to two or more compounds of concern. Consequently, the introduction has been revised to clarify the intended breadth of application.

Several commentators expressed concern that "sufficient similarity" was difficult to define and that the Guidelines should give more details concerning similar mixtures. The Agency agrees and is planning research projects to improve on the definition. Characteristics such as

composition and toxic end-effects are certainly important, but the best indicators of similarity in terms of risk assessment have yet to be determined. The discussion in the Guidelines emphasizes case-by-case judgment until the necessary research can be performed. The Agency considered but rejected adding an example, because it is not likely that any single example would be adequate to illustrate the variety in the data and types of judgments that will be required in applying this concept. Inclusion of examples is being considered for the technical support document.

2.2. MIXTURES OF CARCINOGENS AND SYSTEMIC TOXICANTS

The applicability of the preferred approach for a mixture of carcinogens and systemic (noncarcinogenic) toxicants was a concern of several public commentators as well as the SAB. The Agency realizes that the preferred approach of using test data on the mixture itself may not be sufficiently protective in all cases. For example, take a simple two-component mixture of one carcinogen and one toxicant. The preferred approach would lead to using toxicity data on the mixture of the two compounds. However, it is possible to set the proportions of each component so that in a chronic bioassay of such a mixture, the presence of the toxicant could mask the activity of the carcinogen. That is to say, at doses of the mixture sufficient for the carcinogen to induce tumors in the small experimental group, the toxicant could induce mortality. At a lower dose in the same study, no adverse effects would be observed, including no carcinogenic effects. The data would then suggest use of a threshold approach. Since carcinogenicity is considered by the Agency to be a nonthreshold effect, it may not be prudent to construe the negative results of such a bioassay as indicating the absence of risk at lower doses. Consequently, the Agency has revised the discussion of the preferred approach to allow the risk assessor to evaluate the potential for masking of carcinogenicity or other effects on a case-by-case basis.

Another difficulty occurs with such a mixture when the risk assessment needs to be based on data for the mixture components. Carcinogens and systemic toxicants are evaluated by the Agency using different approaches and generally are described by different types of data: response rates for carcinogens vs. effect descriptions for toxicants. The Agency recognizes this difficulty and recommends research to develop a new assessment model for combining these dissimilar data sets into one risk estimate. One suggestion in the interim is to present separate risk estimates for the dissimilar end points, including carcinogenic, teratogenic, mutagenic, and systemic toxicant components.

3. ADDITIVITY ASSUMPTION

Numerous comments were received concerning the assumption of additivity, including:

- a. the applicability of additivity to “complex” mixtures;
- b. the use of dose additivity for compounds that induce different effects;
- c. the interpretation of the Hazard Index; and
- d. the use of interaction data.

Parts of the discussion in the proposed guidelines concerning the use of additivity assumptions were vague and have been revised in the final Guidelines to clarify the Agency’s intent and position.

3.1. COMPLEX MIXTURES

The issue of the applicability of an assumption of additivity to complex mixtures containing tens or hundreds of components was raised in several of the public comments. The Agency and its reviewers agree that as the number of compounds in the mixture increases, an assumption of additivity will become less reliable in estimating risk. This is based on the fact that each component estimate of risk or an acceptable level is associated with some error and uncertainty. With current knowledge, the uncertainty will increase as the number of components increases. In any event, little experimental data are available to determine the general change in the error as the mixture contains more components. The Agency has decided that a limit to the number of components should not be set in these Guidelines. However, the Guidelines do explicitly state that as the number of compounds in the mixture increases, the uncertainty associated with the risk assessment is also likely to increase.

3.2. DOSE ADDITIVITY

Commentators were concerned about what appeared to be a recommendation of the use of dose additivity for compounds that induce different effects. The discussion following the dose additivity equation was clarified to indicate that the act of combining all compounds, even if they induce dissimilar effects, is a screening procedure and not the preferred procedure in developing a hazard index. The Guidelines were further clarified to state that dose (or response) additivity is theoretically sound, and therefore best applied for assessing mixtures of similar acting components that do not interact.

3.3. INTERPRETATION OF THE HAZARD INDEX

Several comments addressed the potential for misinterpretation of the hazard index, and some questioned its validity, suggesting that it mixes science and value judgments by using “acceptable” levels in the calculation. The Agency agrees with the possible confusion regarding its use and has revised the Guidelines for clarification. The hazard index is an easily derived restatement of dose additivity, and is, therefore, most accurate when used with mixture components that have similar toxic action. When used with components of unknown or dissimilar action, the hazard index is less accurate and should be interpreted only as a rough indication of concern. As with dose addition, the uncertainty associated with the hazard index increases as the number of components increases, so that it is less appropriate for evaluating the toxicity of complex mixtures.

3.4. USE OF INTERACTION DATA

A few commentators suggested that any interaction data should be used to quantitatively alter the risk assessment. The Agency disagrees. The current information on interactions is meager, with only a few studies comparing response to the mixture with that predicted by studies on components. Additional uncertainties include exposure variations due to changes in composition, mixture dose, and species differences in the extent of the interaction. The Agency is constructing an interaction data base in an attempt to answer some of these issues. Other comments concerned the use of different types of interaction data. The Guidelines restrict the use of interaction data to that obtained from whole animal bioassays of a duration appropriate to the risk assessment. Since such data are frequently lacking, at least for chronic or subchronic effects, the issue is whether to allow for the use of other information such as acute data, *in vitro* data, or structure-activity relationships to quantitatively alter the risk assessment, perhaps by use of a safety factor. The Agency believes that sufficient scientific support does not exist for the use of such data in any but a qualitative discussion of possible synergistic or antagonistic effects.

4. UNCERTAINTIES AND THE SUFFICIENCY OF THE DATA BASE

In the last two paragraphs of Section II of the Guidelines, situations are discussed in which the risk assessor is presented with incomplete toxicity, monitoring, or exposure data. The SAB, as well as several public commentators, recommended that the “risk management” tone of this section be modified and that the option of the risk assessor to decline to conduct a risk assessment be made more explicit.

This is a difficult issue that must consider not only the quality of the available data for risk assessment, but also the needs of the Agency in risk management. Given the types of poor

data often available, the risk assessor may indicate that the risk assessment is based on limited information and thus contains no quantification of risk. Nonetheless, in any risk assessment, substantial uncertainties exist. It is the obligation of the risk assessor to provide an assessment, but also to ensure that all the assumptions and uncertainties are articulated clearly and quantified whenever possible.

The SAB articulated several other recommendations related to uncertainties, all of which have been followed in the revision of the Guidelines. One recommendation was that the summary procedure table also be presented as a flow chart so that all options are clearly displayed. The SAB further recommended the development of a system to express the level of confidence in the various steps of the risk assessment.

The Agency has revised the summary table to present four major options: risk assessment using data on the mixture itself, data on a similar mixture, data on the mixture's components, or declining to quantify the risk when the data are inadequate. A flow chart of this table has also been added to more clearly depict the various options and to suggest the combining of the several options to indicate the variability and uncertainties in the risk assessment.

To determine the adequacy of the data, the SAB also recommended the development of a system to express the level of confidence associated with various steps in the risk assessment process. The Agency has developed a rating scheme to describe data quality in three areas: interaction, health effects, and exposure. This classification provides a range of five levels of data quality for each of the three areas. Choosing the last level in any area results in declining to perform a quantitative risk assessment due to inadequate data. These last levels are described as follows:

Interactions: An assumption of additivity cannot be justified, and no quantitative risk assessment can be conducted.

Health effects: A lack of health effects information on the mixture and its components precludes a quantitative risk assessment.

Exposure: The available exposure information is insufficient for conducting a risk assessment.

Several commentors, including the SAB, emphasized the importance of not losing these classifications and uncertainties farther along in the risk management process. The discussion of uncertainties has been expanded in the final Guidelines and includes the recommendation that a

discussion of uncertainties and assumptions be included at every step of the regulatory process that uses risk assessment.

Another SAB comment was that the Guidelines should include additional procedures for mixtures with more than one end point or effect. The Agency agrees that these are concerns and revised the Guidelines to emphasize these as additional uncertainties worthy of further research.

5. NEED FOR A TECHNICAL SUPPORT DOCUMENT

The third major SAB comment concerned the necessity for a separate technical support document for these Guidelines. The SAB pointed out that the scientific and technical background from which these Guidelines must draw their validity is so broad and varied that it cannot reasonably be synthesized within the framework of a brief set of guidelines. The Agency is developing a technical support document that will summarize the available information on health effects from chemical mixtures, and on interaction mechanisms, as well as identify and develop mathematical models and statistical techniques to support these Guidelines. This document will also identify critical gaps and research needs.

Several comments addressed the need for examples on the use of the Guidelines. The Agency has decided to include examples in the technical support document.

Another issue raised by the SAB concerned the identification of research needs. Because little emphasis has been placed on the toxicology of mixtures until recently, the information on mixtures is limited. The SAB pointed out that identifying research needs is critical to the risk assessment process, and the EPA should ensure that these needs are considered in the research planning process. The Agency will include a section in the technical support document that identifies research needs regarding both methodology and data.

Exhibit 27

Meeting January 14 1965

The Environment and Disease: Association or Causation?

by Sir Austin Bradford Hill CBE DSC FRCP(hon) FRS
(Professor Emeritus of Medical Statistics,
University of London)

Amongst the objects of this newly-founded Section of Occupational Medicine are firstly 'to provide a means, not readily afforded elsewhere, whereby physicians and surgeons with a special knowledge of the relationship between sickness and injury and conditions of work may discuss their problems, not only with each other, but also with colleagues in other fields, by holding joint meetings with other Sections of the Society'; and, secondly, 'to make available information about the physical, chemical and psychological hazards of occupation, and in particular about those that are rare or not easily recognized'.

At this first meeting of the Section and before, with however laudable intentions, we set about instructing our colleagues in other fields, it will be proper to consider a problem fundamental to our own. How in the first place do we detect these relationships between sickness, injury and conditions of work? How do we determine what are physical, chemical and psychological hazards of occupation, and in particular those that are rare and not easily recognized?

There are, of course, instances in which we can reasonably answer these questions from the general body of medical knowledge. A particular, and perhaps extreme, physical environment cannot fail to be harmful; a particular chemical is known to be toxic to man and therefore suspect on the factory floor. Sometimes, alternatively, we may be able to consider what *might* a particular environment do to man, and then see whether such consequences are indeed to be found. But more often than not we have no such guidance, no such means of proceeding; more often than not we are dependent upon our observation and enumeration of defined events for which we then seek antecedents. In other words we see that the event B is associated with the environmental feature A, that, to take a specific example, some form of respiratory illness is associated with a dust in the environment. In what circumstances can we pass from this

President's Address

observed *association* to a verdict of *causation*?
Upon what basis should we proceed to do so?

I have no wish, nor the skill, to embark upon a philosophical discussion of the meaning of 'causation'. The 'cause' of illness may be immediate and direct, it may be remote and indirect underlying the observed association. But with the aims of occupational, and almost synonymously preventive, medicine in mind the decisive question is whether the frequency of the undesirable event B will be influenced by a change in the environmental feature A. *How* such a change exerts that influence may call for a great deal of research. However, before deducing 'causation' and taking action we shall not invariably have to sit around awaiting the results of that research. The whole chain may have to be unravelled or a few links may suffice. It will depend upon circumstances.

Disregarding then any such problem in semantics we have this situation. Our observations reveal an association between two variables, perfectly clear-cut and beyond what we would care to attribute to the play of chance. What aspects of that association should we especially consider before deciding that the most likely interpretation of it is causation?

(1) *Strength*. First upon my list I would put the strength of the association. To take a very old example, by comparing the occupations of patients with scrotal cancer with the occupations of patients presenting with other diseases, Percival Pott could reach a correct conclusion because of the *enormous* increase of scrotal cancer in the chimney sweeps. 'Even as late as the second decade of the twentieth century', writes Richard Doll (1964), 'the mortality of chimney sweeps from scrotal cancer was some 200 times that of workers who were not specially exposed to tar or mineral oils and in the eighteenth century the relative difference is likely to have been much greater.'

To take a more modern and more general example upon which I have now reflected for over fifteen years, prospective inquiries into smoking have shown that the death rate from cancer of the lung in cigarette smokers is nine to ten times the rate in non-smokers and the rate in heavy cigarette smokers is twenty to thirty times

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as great. On the other hand the death rate from coronary thrombosis in smokers is no more than twice, possibly less, the death rate in non-smokers. Though there is good evidence to support causation it is surely much easier in this case to think of some features of life that may go hand-in-hand with smoking – features that might conceivably be the real underlying cause or, at the least, an important contributor, whether it be lack of exercise, nature of diet or other factors. But to explain the pronounced excess in cancer of the lung in any other environmental terms requires some feature of life so intimately linked with cigarette smoking and with the amount of smoking that such a feature should be easily detectable. If we cannot detect it or reasonably infer a specific one, then in such circumstances I think we are reasonably entitled to reject the vague contention of the armchair critic ‘you can’t prove it, there may be such a feature’.

Certainly in this situation I would reject the argument sometimes advanced that what matters is the absolute difference between the death rates of our various groups and not the ratio of one to other. That depends upon what we want to know. If we want to know how many extra deaths from cancer of the lung will take place through smoking (i.e. presuming causation), then obviously we must use the absolute differences between the death rates – 0.07 per 1,000 per year in non-smoking doctors, 0.57 in those smoking 1–14 cigarettes daily, 1.39 for 15–24 cigarettes daily and 2.27 for 25 or more daily. But it does not follow here, or in more specifically occupational problems, that this best measure of the effect upon mortality is also the best measure in relation to aetiology. In this respect the ratios of 8, 20 and 32 to 1 are far more informative. It does not, of course, follow that the differences revealed by ratios are of any practical importance. Maybe they are, maybe they are not; but that is another point altogether.

We may recall John Snow’s classic analysis of the opening weeks of the cholera epidemic of 1854 (Snow 1855). The death rate that he recorded in the customers supplied with the grossly polluted water of the Southwark and Vauxhall Company was in truth quite low – 71 deaths in each 10,000 houses. What stands out vividly is the fact that the small rate is 14 times the figure of 5 deaths per 10,000 houses supplied with the sewage-free water of the rival Lambeth Company.

In thus putting emphasis upon the strength of an association we must, nevertheless, look at the obverse of the coin. We must not be too ready to dismiss a cause-and-effect hypothesis merely on

the grounds that the observed association appears to be slight. There are many occasions in medicine when this is in truth so. Relatively few persons harbouring the meningococcus fall sick of meningococcal meningitis. Relatively few persons occupationally exposed to rat’s urine contract Weil’s disease.

(2) *Consistency*: Next on my list of features to be specially considered I would place the *consistency* of the observed association. Has it been repeatedly observed by different persons, in different places, circumstances and times?

This requirement may be of special importance for those rare hazards singled out in the Section’s terms of reference. With many alert minds at work in industry today many an environmental association may be thrown up. Some of them on the customary tests of statistical significance will appear to be unlikely to be due to chance. Nevertheless whether chance is the explanation or whether a true hazard has been revealed may sometimes be answered only by a repetition of the circumstances and the observations.

Returning to my more general example, the Advisory Committee to the Surgeon-General of the United States Public Health Service found the association of smoking with cancer of the lung in 29 retrospective and 7 prospective inquiries (US Department of Health, Education & Welfare 1964). The lesson here is that broadly the same answer has been reached in quite a wide variety of situations and techniques. In other words we can justifiably infer that the association is not due to some constant error or fallacy that permeates every inquiry. And we have indeed to be on our guard against that.

Take, for instance, an example given by Heady (1958). Patients admitted to hospital for operation for peptic ulcer are questioned about recent domestic anxieties or crises that may have precipitated the acute illness. As controls, patients admitted for operation for a simple hernia are similarly quizzed. But, as Heady points out, the two groups may not be *in pari materia*. If your wife ran off with the lodger last week you still have to take your perforated ulcer to hospital without delay. But with a hernia you might prefer to stay at home for a while – to mourn (or celebrate) the event. No number of exact repetitions would remove or necessarily reveal that fallacy.

We have, therefore, the somewhat paradoxical position that the different results of a different inquiry certainly cannot be held to refute the

original evidence; yet the same results from precisely the same form of inquiry will not invariably greatly strengthen the original evidence. I would myself put a good deal of weight upon similar results reached in quite different ways, e.g. prospectively and retrospectively.

Once again looking at the obverse of the coin there will be occasions when repetition is absent or impossible and yet we should not hesitate to draw conclusions. The experience of the nickel refiners of South Wales is an outstanding example. I quote from the Alfred Watson Memorial Lecture that I gave in 1962 to the Institute of Actuaries:

'The population at risk, workers and pensioners, numbered about one thousand. During the ten years 1929 to 1938, sixteen of them had died from cancer of the lung, eleven of them had died from cancer of the nasal sinuses. At the age specific death rates of England and Wales at that time, one might have anticipated one death from cancer of the lung (to compare with the 16), and a fraction of a death from cancer of the nose (to compare with the 11). In all other bodily sites cancer had appeared on the death certificate 11 times and one would have expected it to do so 10-11 times. There had been 67 deaths from all other causes of mortality and over the ten years' period 72 would have been expected at the national death rates. Finally division of the population at risk in relation to their jobs showed that the excess of cancer of the lung and nose had fallen wholly upon the workers employed in the chemical processes.

'More recently my colleague, Dr Richard Doll, has brought this story a stage further. In the nine years 1948 to 1956 there had been, he found, 48 deaths from cancer of the lung and 13 deaths from cancer of the nose. He assessed the numbers expected at normal rates of mortality as, respectively 10 and 0.1.

'In 1923, long before any special hazard had been recognized, certain changes in the refinery took place. No case of cancer of the nose has been observed in any man who first entered the works after that year, and in these men there has been no excess of cancer of the lung. In other words, the excess in both sites is uniquely a feature in men who entered the refinery in, roughly, the first 23 years of the present century.

'No causal agent of these neoplasms has been identified. Until recently no animal experimentation had given any clue or any support to this wholly statistical evidence. Yet I wonder if any of us would hesitate to accept it as proof of a grave industrial hazard?' (Hill 1962).

In relation to my present discussion I know of no parallel investigation. We have (or certainly had) to make up our minds on a unique event; and there is no difficulty in doing so.

(3) *Specificity*: One reason, needless to say, is the specificity of the association, the third characteristic which invariably we must consider. If, as here, the association is limited to specific workers and to particular sites and types of disease and there is no association between the work and other modes of dying, then clearly that is a strong argument in favour of causation.

We must not, however, over-emphasize the importance of the characteristic. Even in my present example there is a cause and effect relationship with two different sites of cancer – the lung and the nose. Milk as a carrier of infection and, in that sense, the cause of disease can produce such a disparate galaxy as scarlet fever, diphtheria, tuberculosis, undulant fever, sore throat, dysentery and typhoid fever. Before the discovery of the underlying factor, the bacterial origin of disease, harm would have been done by pushing too firmly the need for specificity as a necessary feature before convicting the dairy.

Coming to modern times the prospective investigations of smoking and cancer of the lung have been criticized for not showing specificity – in other words the death rate of smokers is higher than the death rate of non-smokers from many causes of death (though in fact the results of Doll & Hill, 1964, do not show that). But here surely one must return to my first characteristic, the strength of the association. If other causes of death are raised 10, 20 or even 50% in smokers whereas cancer of the lung is raised 900-1,000% we have specificity – a specificity in the magnitude of the association.

We must also keep in mind that diseases may have more than one cause. It has always been possible to acquire a cancer of the scrotum without sweeping chimneys or taking to mule-spinning in Lancashire. One-to-one relationships are not frequent. Indeed I believe that multi-causation is generally more likely than single causation though possibly if we knew all the answers we might get back to a single factor.

In short, if specificity exists we may be able to draw conclusions without hesitation; if it is not apparent, we are not thereby necessarily left sitting irresolutely on the fence.

(4) *Temporality*: My fourth characteristic is the temporal relationship of the association – which is the cart and which the horse? This is a question which might be particularly relevant with diseases of slow development. Does a particular diet lead to disease or do the early stages of the disease lead to those peculiar dietetic habits? Does a

particular occupation or occupational environment promote infection by the tubercle bacillus or are the men and women who select that kind of work more liable to contract tuberculosis whatever the environment – or, indeed, have they already contracted it? This temporal problem may not arise often but it certainly needs to be remembered, particularly with selective factors at work in industry.

(5) *Biological gradient*: Fifthly, if the association is one which can reveal a biological gradient, or dose-response curve, then we should look most carefully for such evidence. For instance, the fact that the death rate from cancer of the lung rises linearly with the number of cigarettes smoked daily, adds a very great deal to the simpler evidence that cigarette smokers have a higher death rate than non-smokers. That comparison would be weakened, though not necessarily destroyed, if it depended upon, say, a much heavier death rate in light smokers and a lower rate in heavier smokers. We should then need to envisage some much more complex relationship to satisfy the cause-and-effect hypothesis. The clear dose-response curve admits of a simple explanation and obviously puts the case in a clearer light.

The same would clearly be true of an alleged dust hazard in industry. The dustier the environment the greater the incidence of disease we would expect to see. Often the difficulty is to secure some satisfactory quantitative measure of the environment which will permit us to explore this dose-response. But we should invariably seek it.

(6) *Plausibility*: It will be helpful if the causation we suspect is biologically plausible. But this is a feature I am convinced we cannot demand. What is biologically plausible depends upon the biological knowledge of the day.

To quote again from my Alfred Watson Memorial Lecture (Hill 1962), there was

‘... no biological knowledge to support (or to refute) Pott’s observation in the 18th century of the excess of cancer in chimney sweeps. It was lack of biological knowledge in the 19th that led a prize essayist writing on the value and the fallacy of statistics to conclude, amongst other “absurd” associations, that “it could be no more ridiculous for the stranger who passed the night in the steerage of an emigrant ship to ascribe the typhus, which he there contracted, to the vermin with which bodies of the sick might be infected”. And coming to nearer times, in the 20th century there was no biological knowledge to support the evidence against rubella.’

In short, the association we observe may be one new to science or medicine and we must not dismiss it too light-heartedly as just too odd. As Sherlock Holmes advised Dr Watson, ‘when you have eliminated the impossible, whatever remains, however improbable, must be the truth.’

(7) *Coherence*: On the other hand the cause-and-effect interpretation of our data should not seriously conflict with the generally known facts of the natural history and biology of the disease – in the expression of the Advisory Committee to the Surgeon-General it should have coherence.

Thus in the discussion of lung cancer the Committee finds its association with cigarette smoking coherent with the temporal rise that has taken place in the two variables over the last generation and with the sex difference in mortality – features that might well apply in an occupational problem. The known urban/rural ratio of lung cancer mortality does not detract from coherence, nor the restriction of the effect to the lung.

Personally, I regard as greatly contributing to coherence the histopathological evidence from the bronchial epithelium of smokers and the isolation from cigarette smoke of factors carcinogenic for the skin of laboratory animals. Nevertheless, while such laboratory evidence can enormously strengthen the hypothesis and, indeed, may determine the actual causative agent, the lack of such evidence cannot nullify the epidemiological observations in man. Arsenic can undoubtedly cause cancer of the skin in man but it has never been possible to demonstrate such an effect on any other animal. In a wider field John Snow’s epidemiological observations on the conveyance of cholera by the water from the Broad Street pump would have been put almost beyond dispute if Robert Koch had been then around to isolate the vibrio from the baby’s nappies, the well itself and the gentleman in delicate health from Brighton. Yet the fact that Koch’s work was to be awaited another thirty years did not really weaken the epidemiological case though it made it more difficult to establish against the criticisms of the day – both just and unjust.

(8) *Experiment*: Occasionally it is possible to appeal to experimental, or semi-experimental, evidence. For example, because of an observed association some preventive action is taken. Does it in fact prevent? The dust in the workshop is reduced, lubricating oils are changed, persons stop smoking cigarettes. Is the frequency of the associated events affected? Here the strongest

support for the causation hypothesis may be revealed.

(9) *Analogy*: In some circumstances it would be fair to judge by analogy. With the effects of thalidomide and rubella before us we would surely be ready to accept slighter but similar evidence with another drug or another viral disease in pregnancy.

Here then are nine different viewpoints from all of which we should study association before we cry causation. What I do not believe – and this has been suggested – is that we can usefully lay down some hard-and-fast rules of evidence that *must* be obeyed before we accept cause and effect. None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*. What they can do, with greater or less strength, is to help us to make up our minds on the fundamental question – is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?

Tests of Significance

No formal tests of significance can answer those questions. Such tests can, and should, remind us of the effects that the play of chance can create, and they will instruct us in the likely magnitude of those effects. Beyond that they contribute nothing to the 'proof' of our hypothesis.

Nearly forty years ago, amongst the studies of occupational health that I made for the Industrial Health Research Board of the Medical Research Council was one that concerned the workers in the cotton-spinning mills of Lancashire (Hill 1930). The question that I had to answer, by the use of the National Health Insurance records of that time, was this: Do the workers in the cardroom of the spinning mill, who tend the machines that clean the raw cotton, have a sickness experience in any way different from that of other operatives in the same mills who are relatively unexposed to the dust and fibre that were features of the cardroom? The answer was an unqualified 'Yes'. From age 30 to age 60 the cardroom workers suffered over three times as much from respiratory causes of illness whereas from non-respiratory causes their experience was not different from that of the other workers. This pronounced difference with the respiratory causes was derived not from abnormally long periods of sickness but rather from an excessive number of repeated absences from work of the cardroom workers.

All this has rightly passed into the limbo of forgotten things. What interests me today is this: My results were set out for men and women separately and for half a dozen age groups in 36 tables. So there were plenty of sums. Yet I cannot find that anywhere I thought it necessary to use a test of significance. The evidence was so clear-cut, the differences between the groups were mainly so large, the contrast between respiratory and non-respiratory causes of illness so specific, that no formal tests could really contribute anything of value to the argument. So why use them?

Would we think or act that way today? I rather doubt it. Between the two world wars there was a strong case for emphasizing to the clinician and other research workers the importance of not overlooking the effects of the play of chance upon their data. Perhaps too often generalities were based upon two men and a laboratory dog while the treatment of choice was deduced from a difference between two bedfuls of patients and might easily have no true meaning. It was therefore a useful corrective for statisticians to stress, and to teach the need for, tests of significance merely to serve as guides to caution before drawing a conclusion, before inflating the particular to the general.

I wonder whether the pendulum has not swung too far – not only with the attentive pupils but even with the statisticians themselves. To decline to draw conclusions without standard errors can surely be just as silly? Fortunately I believe we have not yet gone so far as our friends in the USA where, I am told, some editors of journals will return an article because tests of significance have not been applied. Yet there are innumerable situations in which they are totally unnecessary – because the difference is grotesquely obvious, because it is negligible, or because, whether it be formally significant or not, it is too small to be of any practical importance. What is worse the glitter of the *t* table diverts attention from the inadequacies of the fare. Only a tithe, and an unknown tithe, of the factory personnel volunteer for some procedure or interview, 20% of patients treated in some particular way are lost to sight, 30% of a randomly-drawn sample are never contacted. The sample may, indeed, be akin to that of the man who, according to Swift, 'had a mind to sell his house and carried a piece of brick in his pocket, which he showed as a pattern to encourage purchasers'. The writer, the editor and the reader are unmoved. The magic formulæ are there.

Of course I exaggerate. Yet too often I suspect we waste a deal of time, we grasp the shadow and

lose the substance, we weaken our capacity to interpret data and to take reasonable decisions whatever the value of P . And far too often we deduce 'no difference' from 'no significant difference'. Like fire, the χ^2 test is an excellent servant and a bad master.

The Case for Action

Finally, in passing from association to causation I believe in 'real life' we shall have to consider what flows from that decision. On scientific grounds we should do no such thing. The evidence is there to be judged on its merits and the judgment (in that sense) should be utterly independent of what hangs upon it – or who hangs because of it. But in another and more practical sense we may surely ask what is involved in our decision. In occupational medicine our object is usually to take action. If this be operative cause and that be deleterious effect, then we shall wish to intervene to abolish or reduce death or disease.

While that is a commendable ambition it almost inevitably leads us to introduce differential standards before we convict. Thus on relatively slight evidence we might decide to restrict the use of a drug for early-morning sickness in pregnant women. If we are wrong in deducing causation from association no great harm will be done. The good lady and the pharmaceutical industry will doubtless survive.

On fair evidence we might take action on what appears to be an occupational hazard, e.g. we might change from a probably carcinogenic oil

to a non-carcinogenic oil in a limited environment and without too much injustice if we are wrong. But we should need very strong evidence before we made people burn a fuel in their homes that they do not like or stop smoking the cigarettes and eating the fats and sugar that they do like. In asking for very strong evidence I would, however, repeat emphatically that this does not imply crossing every 't', and swords with every critic, before we act.

All scientific work is incomplete – whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time.

Who knows, asked Robert Browning, but the world may end tonight? True, but on available evidence most of us make ready to commute on the 8.30 next day.

REFERENCES

- Doll R (1964) In: *Medical Surveys and Clinical Trials*. Ed. L J Witts. 2nd ed. London: p 333
Doll R & Hill A B (1964) *Brit. med. J.* i, 1399, 1460
Heady J A (1958) *Med. World, Lond.* 89, 305
Hill A B
(1930) Sickness amongst Operatives in Lancashire Spinning Mills. Industrial Health Research Board Report No. 59. HMSO, London
(1962) *J. Inst. Actu.* 88, 178
Snow J (1855) *On the Mode of Communication of Cholera*. 2nd ed. London (Reprinted 1936, New York)
US Department of Health, Education & Welfare (1964) *Smoking and Health*. Public Health Service Publication No. 1103. Washington

Exhibit 28



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REVIEWS AND COMMENTARIES

Biologic Plausibility in Causal Inference: Current Method and Practice

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The primary prevention of human cancer relies on the idea that reducing a population's exposure to a causal risk factor will result in decreased cancer incidence (1). Among the many examples (2–4), perhaps the most familiar is cigarette smoking and lung cancer (5), declared a causal association in 1964 and for years the focus of public health interventions (6). Not all associations, of course, are causal, and not all exposure-cancer pairs are statistically associated. Hundreds, perhaps thousands of exposures have been studied, including infectious agents, environmental and occupational exposures, lifestyle factors (including diet), medications, and medical technologies. Some are now considered causal risk factors, others remain controversial (7). Still other exposures are no longer studied due to empirical refutation, evidence judged to be insufficient, or changes in research funding priorities.

An important step along the path from research on potential cancer-causing exposures to successful application of preventive interventions is an assessment of available evidence, which typically takes place in review papers and editorials, and is often referred to as causal inference. Causal conclusions, or causal judgments, are one result of the qualitative criteria-based causal inference methods used in these assessments (8,

9). Two closely-related sets of criteria remain the foundation for the current practice of causal inference: those proposed by the Surgeon General's committee in 1964 (10) and those described by Austin Bradford Hill in 1965 (11).

Advances in the biologic sciences and their integration with public health science in molecular epidemiology (12–19) make one causal criterion, biologic plausibility (sometimes called biologic coherence), an increasingly important consideration in causal inference. Despite the growing influence of this criterion, there has been little systematic study of the concept of biologic plausibility and almost nothing published about how it is used in the practice of causal inference.

In this commentary, we review the role of biologic plausibility in causal inference as described in the methodological literature, and then review how biologic plausibility is used in practice, i.e., in review papers assessing evidence on specific associations (smoking and cervical cancer, and vasectomy and prostate cancer). These represent a small fraction of associations relevant to cancer prevention, yet in each case, considerable interest has been generated regarding the biologic plausibility of the underlying causal hypothesis.

Our purpose is primarily to describe how the concept of plausibility is currently used—and how methodologists recommend that it be used. This will serve as a first step toward more detailed inquiries into central unanswered questions (20, 21), such as: How does a *plausible* mechanism differ from a *known* mechanism? How much and what kinds of biologic evidence are important in judging the plausibility of an association? How will advances in measurement technology and in our understanding of the cellular pro-

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Abbreviations: CI, confidence interval; IARC, International Agency for Research on Cancer.

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cesses involved in initiation and tumor promotion change the way the criterion of biologic plausibility is interpreted and used? Because biologic plausibility is only one of several considerations important in making causal judgments, we are cautious not to make our own causal conclusions regarding the associations studied. We will, however, make some recommendations regarding the future role of biologic plausibility in the theory and practice of causal inference.

Background: biologic plausibility in theory and methodology

An account of the role of biology in causal inference could begin about a century and a half ago with the works of Jakob Henle and his student, Robert Koch (22). The “Henle-Koch” postulates were an early description of empirically-based conditions for causes of infectious diseases and later became the starting point for discussions of causation in chronic diseases. In epidemiology, these discussions began in earnest in the 1950s, and from them two papers emerged in the mid-1960s which have had a sustained impact on the practice of causal inference in cancer epidemiology (9). In 1964, a US Surgeon General’s committee used a set of five criteria to judge that smoking cigarettes caused lung cancer (10). One year later, Bradford Hill expanded this list to nine criteria—he called them “aspects of associations”—important to disease causation (11).

Both early accounts included a role for biology in causal inference. Coherence was the criterion of the Surgeon General’s committee that incorporated the related notions of biologic mechanism and biologic plausibility. The approach is succinctly described in the committee’s own wording:

“Coherence is clearly established when the actual mechanism of disease is defined. Coherence exists, nevertheless, although of a lesser magnitude, when there is enough evidence to support a plausible mechanism, but not a detailed understanding of each step in the chain of events by which a given etiologic agent produces disease” (10, p. 20).

Hill distinguished between coherence and plausibility, although his views on the latter have been more influential in cancer epidemiology (23). Hill wrote:

“It will be helpful if the cause. . . is biologically plausible. . . but we cannot demand it. What is biologically plausible depends upon the biological knowledge of the day” (11, p. 298).

Hill’s words are echoed in a recent *Lancet* commentary by Glynn:

“The existence of a suggested mechanism by which a proposed cause of a disease exerts its effect is reas-

suring. However, this will depend on the biological knowledge of the disease at the time. . .” (24, p. 531).

Hill’s and Glynn’s papers (11, 24), and many others published between 1965 and 1994 (25–32), reveal a commonly-held viewpoint, that in a given case (i.e., for a single factor-cancer association) *a biologically plausible association is one for which a reasonable mechanism can be hypothesized, but for which no biologic evidence may exist*. As such, biologic plausibility becomes a dispensable consideration. In support of this view, Schlesselman argues that biologic plausibility “may occasionally impede acceptance of new facts” and is a “conservative” criterion, used “either to dismiss some unexpected finding or to support an association from a study based on suspect methods” (29, p. 201). The dispensability of biologic plausibility also figures in decisions to publish the results of epidemiologic studies in some journals. An editor of the *New England Journal of Medicine* recently wrote that publication may be warranted for large effects that “do not make biologic sense” (33, p. 824). Note, however, that the endpoint is publication (not causation), and that a condition has been placed on at least one other causal criterion—here, magnitude of the association—in order to justify dispensing with biologic plausibility.

The rapid progress made in the fields of molecular biology and molecular epidemiology since the late 1980s has underscored a second way to represent biologic plausibility in causal inference (19, 34–38). *Many authors have argued that simply suggesting a mechanism for a factor-cancer association is insufficient. Evidence supporting the proposed mechanism is also necessary*. The International Agency for Research on Cancer (IARC), in a 1990 monograph, categorizes types of biologically relevant evidence (35). Emphasized are biologic indicators of exposure, such as DNA adducts or protein adducts and animal model evidence. In a recent paper, McMichael (19) examines the current capacity of molecular epidemiologic techniques to identify the biologically effective dose at tissue targets (e.g., DNA adducts), early biologic effects (e.g., mutations), and variations in individual susceptibility. He argues that evidence of prospective links between molecular events, especially DNA adducts and cancer occurrence, are important in causal assessments yet are rarely available. With regard to animal evidence (e.g., long-term bioassays in rodents), the IARC monograph discusses the strengths and limitations of this type of evidence, particularly the interspecies differences in susceptibility to chemically induced cancer and the extent to which genetic heterogeneity and other factors can be controlled.

A third, more rigorous, notion of biologic plausibility has also been proposed: *an association is considered biologically plausible if there is sufficient evidence to show how the factor influences a known disease mechanism* (30, 37). This is the most stringent of the three approaches to biologic plausibility relative to the “evidence-free” or “evidence-supportive” notions discussed above because it requires that the mechanism be defined to the extent that it is possible to examine the influence of the putative factor on the inner workings of that mechanism.

These three approaches help to organize the methodological work to date and reveal vastly different opinions on what counts as a biologically plausible association. It remains unclear how much and what kinds of evidence will turn a “suggested” (24) or “hypothesized” (36) mechanism into a “coherent” mechanism (10), i.e., one that not only “makes sense” (33) but one “defined. . . by our detailed understanding of each step in the chain of events” (10, p. 20). Similarly, what does it take to claim that we “know” a mechanism (30, 37)? We continue our search for answers to these central questions on the role of biologic evidence in human cancer causation not by proposing more theory (39, 40), but, rather, by examining two well-known exposure-cancer associations. For each we describe the evolution of evidence and the ways in which investigators, specifically those publishing review papers, have approached the concepts of biologic evidence, plausibility, and mechanism in causal inference.

Materials and methods

The MEDLINE[®] database was searched from January 1977 through December 1996, using keywords, “causation,” “causal inference,” “biologic plausibility,” “biologic mechanism,” “smoking and cervical cancer,” “and vasectomy and prostate cancer.” Reviews, editorials, and methodological articles were also identified from reference lists of primary research studies and from chapters of general epidemiology, cancer epidemiology, and cancer prevention and control textbooks. In addition, tables of contents from major medical, public health, cancer, and epidemiology journals available at the National Institutes of Health were examined.

Smoking and cervical cancer

Thirty-six case-control and six cohort studies on smoking and cervical cancer were published from 1966 through 1995 (41–83). Ten reviews (84–93), 12 mini-reviews (94–105), two meta-analyses (106, 107), and several related letters and commentaries have also

appeared (108–110). We examined the 10 reviews and two meta-analyses published between 1977 and 1991, divided into three groups: 1977–1984, 1985–1986, and 1989–1991. Next we examined the “mini-reviews” published from 1991 through 1995; these are brief reviews of the association included within reviews of cervical cancer epidemiology, risk factors for gynecologic tumors, or reviews of the impact of smoking on cancer.

Reviews of smoking and cervical cancer (1977–1984). Winkelstein (84) suggested a possible association between smoking and cervical cancer in 1977 (84). Two biologic hypotheses were proposed: First, cervix cancer is primarily a squamous cell disease and smoking causes squamous cell carcinomas in many sites, including lung. Second, smoking constituents (especially carcinogens) may be transported to distant sites (including the cervical epithelium) via the circulation. No evidence was cited for either hypothesis. In 1981, however, Winkelstein (108) noted in a letter written in response to a charge that the association was implausible, findings of nicotine in the breast fluid of nonlactating smokers (111). In 1982, the Surgeon General’s office reviewed the smoking and cervical cancer literature, concluding that it was unclear if an association existed (85). The report ignored the issue of biologic plausibility. One year later, Austin’s review (86) cited epidemiologic evidence along with two studies regarding biologic plausibility: the study showing nicotine in breast fluid (111) mentioned above, and a study showing that inhaled mutagens are concentrated in the urine of smokers (112). Austin argued that “these studies adequately illustrate that epithelial cells must be perfused with smoke carcinogens via the circulation” (86, p. 516) and he declared that cervical cancer was caused by smoking and that preventive measures were needed. Finally, in 1984, Winkelstein et al. published a review whose stated purpose was to “examine the reluctance to accept an etiologic interpretation of the. . . association” (87, p. 2). They added a study showing mutagenicity of smokers’ nipple aspirates (113) and concluded that there was strong evidence to consider smoking a risk factor for cervical cancer.

It is reasonable to conclude that in these early reviews of the smoking and cervical cancer association, biologic plausibility was used (86, 87) as a criterion for which evidence directly testing the biologic hypothesis was unnecessary to make a causal claim, consistent with the “evidence-free” approach mentioned above. Winkelstein et al. (87) and Austin (86) claimed that smoking caused cervical cancer with no direct evidence that smoking constituents reach the

cervical epithelium much less were responsible for carcinogenic changes.

Reviews of smoking and cervical cancer (1985–1986). Three reviews appeared during the years 1985–1986 (88–90). The IARC concluded—without reference to biologic plausibility—that “. . . the causal nature of the association. . . remains uncertain” (88, p. 298). The review also mentioned an alternative hypothesis, that “there is a specific causal agent—an infective agent transmitted sexually” (88, p. 298) so far unidentified. The two reviews published in 1986 also mentioned this possibility, although both maintained that smoking was an independent causal factor (89, 90). With regard to biologic plausibility, both 1986 reviews cited evidence published a year earlier in the *New England Journal of Medicine* (114) showing concentrated nicotine and cotinine levels in the cervical mucus of smokers, thus providing the first direct biologic evidence of exposure to the cervix. In addition, Winkelstein (89) demonstrated that most cervical cancer is squamous, using Third National Cancer Survey data. Finally, the review by Singer and Tay (90 p. S89) argued that smoking may elicit a local immunosuppressive effect facilitating a persistent viral infection. They cited their own unpublished research and a paper describing reduced killer cell activity in male melanoma patients (115).

In terms of evidence-based biologic plausibility, the causal conclusions so strongly argued by Winkelstein (89) and by Singer and Tay (90) are based on a single study documenting that the target tissue is perfused with some chemicals arising from exposure to cigarette smoke. Interestingly, the IARC report mentioned this same biologic study in a separate section of its monograph, yet did not refer to it when concluding that causation was uncertain.

Reviews and meta-analyses of smoking and cervical cancer (1989–1991). By the time new reviews appeared in 1989 (91, 92), two major biologic hypotheses had emerged: that smoking causes cervical cancer by direct exposure of carcinogens to the cervical epithelium, and that smoking induces a local immunosuppressive effect facilitating a persistent viral infection. The Surgeon General’s 1989 (91) review addressed only the direct exposure hypothesis, citing the 1985 *New England Journal of Medicine* study of nicotine and cotinine levels (114) and a study published 1 year later showing mutagenicity of cervical mucus in smokers (116). The report concluded that the association was consistent and plausible but did not claim causation. Later in 1989, Layde (92) also ignored the immunosuppression hypothesis, citing the now-familiar *New England Journal of Medicine* 1985 study (114) and a study confirming the finding that cervical

mucus in smokers is mutagenic (117). Layde reviewed the IARC (88) and the Surgeon General’s (91) decisions, claiming that confounding by an unknown yet likely viral factor was responsible for the cautious decisions found there. He concluded with a public health recommendation that women should stop smoking for many reasons (besides avoiding risk of cervical cancer).

Three papers appeared in 1990, a meta-analysis (106), a review (93), and a commentary on the review (109). The meta-analysis examined six case-control studies of histologically confirmed invasive cervical cancer. The summary odds ratio for current smokers was 1.81 (confidence interval (CI) 1.54–2.12) with no significantly elevated risk in former smokers. Without reference to biologic plausibility, the authors concluded that the “results provide additional rationale for health care professionals. . . to give antismoking messages to their patients” (109, p. 280).

Winkelstein’s fourth review on this topic (93) featured a discussion of the 15 epidemiologic studies published since his 1986 review (89) and an extended discussion of biologic plausibility. Winkelstein reiterated three biologic hypotheses: that smoking-related cancers (including cervical cancer) are squamous, that carcinogenic chemicals in smoke reach the cervical epithelium, and that smoking may act as a cofactor with a viral agent. To buttress the first of these, Winkelstein added findings from a study done in 1962 (118) showing that smoking-related cancers occur as second primaries more frequently in women with primary cancer of the cervix than nonsmoking related cancers (87). Evidence of smoke constituents in cervical epithelium (117, 119) was included for the direct exposure hypothesis. Winkelstein’s treatment of the immunosuppressive hypothesis included four studies from the late 1980s (120–123) including a study (123) showing reductions in Langerhans cells in smokers with normal cervical epithelium and in smokers positive for human papilloma virus infection. To these three hypotheses, Winkelstein added a fourth: that smokers’ lower serum β -carotene levels, perhaps from a deficiency of dietary vitamin A, may increase susceptibility to carcinogens. He noted that the epidemiologic evidence regarding this hypothesis was “equivocal” and offered no biologic evidence. In his conclusion, Winkelstein argued that “cervical cancer should be added to the list of smoking-related diseases” (93, p. 955) and that disease control strategies should include considerations of the etiologic role of cigarette smoking. In response to Winkelstein’s review, Brinton argued that causality was uncertain due to three issues: confounding (by the effects of human papillomavirus infection), effect modification (by di-

etary factors), and the lack of information regarding biologic mechanisms (109). Indeed, Brinton emphasized that “caution must be exercised with regard to biologic plausibility” (109, p. 959) although she acknowledged that the smoking effect could be due to direct exposure or to immunosuppression.

Finally, in 1991, Sood (107) published a meta-analysis of eight case-control studies; the overall odds of cervical cancer was 1.42 (CI 1.33–1.51). With two references to the direct exposure biologic hypothesis (114, 116), Sood concluded that “smoking cessation advice to reduce the risk of all cancer, including perhaps cervical cancer, seems justified” (107, p. 211).

It is reasonable to conclude that during 1989–1991 the authors of reviews and meta-analyses were highly selective in their choice of biologic hypotheses and the evidence cited to support them. Of the six papers examined, four (91, 92, 106, 107) completely ignored the so-called “immunosuppressive” hypothesis. Indeed, one reviewer made public health recommendations without considering any biologic hypothesis (106). Finally, in the 1990 review (93) and accompanying commentary (109), the authors made different causal judgments from the same set of biologic hypotheses and similar evidence, with Winkelstein advising action and Brinton caution.

Biologic evidence and mini-reviews (1992–1995). No full review was published on the smoking and cervical cancer association after 1990. Nevertheless, several studies examining biologic hypotheses (124–132) and several “mini-reviews” (98–103) appeared between 1990 and 1995. In this section, we describe how the “mini-reviews” handled the issue of biologic plausibility in the face of accumulating biologic evidence. Studies confirming elevated nicotine levels in smokers’ and passive smokers’ cervical mucus samples appeared in 1991 (124) and 1992 (126), respectively. Studies showing that smoking increases exfoliation of cervicovaginal epithelial cells, and a follow-up study showing that smoking was not related to mutagenicity of cervical mucus, were published in 1992 (125) and 1993 (128), respectively. Then, in 1993, two studies revealed elevated smoking-related DNA adducts in cervical epithelium (129, 130), evidence which an epidemiologic commentator (19) noted strengthened the biologic plausibility of the association.

Yet not one of the three mini-reviews published in 1995 cited the DNA adduct evidence. Daly et al. (103) cited two studies of cervical mutagenicity published in 1987 and 1988, respectively (regarding the direct exposure hypothesis), as well as one study regarding the immunosuppressive hypothesis (123). Bornstein et al. (104) cited three late 1980s studies of the direct ex-

posure hypothesis (114, 116, 117). Shopland (105) cited no biologic evidence. Earlier mini-reviews (100–102), published too early to have the 1995 DNA adduct evidence available, cited, among them, exactly one study regarding biologic plausibility: the 1988 Hellberg et al. study showing mutagenicity of cervical mucus (117).

Summary findings. Overall, many reviewers ignored some or all of the biologic hypotheses (and the available biologic evidence). Reviewers apparently used different definitions of “biologic plausibility” in their assessments, although no reviewer stated up front how much evidence and what types “count” in making causal judgments. In terms of the three approaches to biologic plausibility discussed in the earlier methodology section of this commentary, many reviewers inferred causation without biologic evidence to support the hypothesis. At least one reviewer (109) appeared to have a more stringent definition for biologic plausibility. No reviewer mentioned, much less described, an underlying model of carcinogenesis and the way in which the biologic evidence cited related to various steps or processes within that model.

The extent to which these findings are generally representative of the use of the criterion of biologic plausibility in the practice of causal inference in epidemiology is an interesting question. To help answer it, we turn to another association, vasectomy and prostate cancer.

Vasectomy and prostate cancer

Studies of morbidity and mortality rates in vasectomized men appeared in the late 1970s and early 1980s (133–136), and three case-control studies (137–139) and a cohort study (140) had also been published in the 1980s. Of these, one case-control study (138) anticipated the concern about a possible relation between vasectomy and prostate cancer. That concern was fostered in 1990 after two positive case-control studies (141, 142) and an accompanying commentary (143) appeared in the *American Journal of Epidemiology*. The studies revealed statistically significant though modest evidence of an association. Soon thereafter, opinion papers appeared from the American Urological Association (144) and from a meeting of the World Health Organization (145) convened to examine the safety of vasectomy. Since 1991, five additional case-control studies have appeared (146–150) and seven reports from six separate cohort studies have been published (151–157). In addition, over 20 publications—editorials, reviews, mini-reviews, and papers specifically focussed on the issue of biologic mechanisms—have appeared (143, 145, 148–177).

The ways in which biologic plausibility and the closely related notion of biologic mechanisms were used in these publications published between 1990 and 1995 exactly parallel the situation in the smoking and cervical cancer literature with one important exception. As before, reviewers selectively examined biologic hypotheses and the biologic evidence available. Some reviewers, for example, mentioned only the possibility that vasectomy might raise testosterone levels. Others examined as many as four different biologic mechanisms: endocrine effects, antisperm antibodies, secretory flow effects, and growth factor inhibitors (167). For any given explanation (i.e., mechanism) the extent of evidence cited varied considerably. Furthermore, no reviewer discussed how he or she approached the concept of biologic plausibility nor described rules of inference for this important causal criterion. In contrast to the smoking and cervical cancer example, however, no reviewer of the vasectomy and prostate cancer association made a causal claim. Indeed, lack of convincing biologic evidence for any of several mechanisms was a common argument against assigning causality (or even risk factor status) to the surgical procedure regardless of the epidemiologic study results.

Discussion

These two examples, involving causal assessments of well publicized associations in peer-reviewed review papers, reveal a large variability in how much attention reviewers devote to existing biologic hypotheses and evidence. Nothing remotely resembling a coherent set of rules for judging biologic evidence appears. Certainly, no reviewer specified a rule for using biologic plausibility as a causal criterion beyond that which is implied from occasional references to Hill's early papers or other similarly nonspecific approaches. This lack of methodological specification mirrors the general practice of causal inference inasmuch as reviewers rarely (if ever) propose in advance what specific rules they use when judging causation (23). Part of the problem, of course, is that for biologic plausibility we suspect that no comprehensive set of rules have *ever* been proposed, in practice or in theory.

Careful consideration of several issues will be necessary to make progress in this important area. Improving the quality of literature reviews and meta-analyses (178, 179) is a first step. Comprehensively examining and summarizing the conclusions of existing reviews, including conclusions about biologic plausibility, is part of a high quality (i.e., systematic) review paper. All previously proposed potential biologic explanations (i.e., mechanisms) would be available to the reviewer. Of course, reviewers may wish to

propose a new mechanism or may exclude one or another biologic hypothesis. In a systematic review, however, reasons for exclusions are made specific in the methods section, e.g., that a hypothesis is not considered because no evidence is available.

Another component of a high quality review is stating how (and with what criteria and evidentiary rules) causal assessments will be made, but we have already discussed the lack of specification of such rules in the methodological literature and in practice. Indeed, we recognize that making judgments about specific exposure-cancer associations may be partially dependent upon the specifics of the situation; an exposure-cancer association, for example, may have unique biologic characteristics requiring unique decisions. On the other hand, if cancer has core processes that are near universal (i.e., occurring with limited variation across many tumor types) then general rules may be possible and obviously useful. Such rules will likely emerge from our expanding understanding of the nature of cancer biology combined with general theories of scientific reasoning and methodology.

It is beyond the purview of this commentary to carefully explore the theoretical foundations of contemporary biologic science as a first step toward proposing new rules of inference for the criterion of biologic plausibility. Nevertheless, a discussion of biologic mechanism and its role in scientific explanation may pave the way for a more detailed inquiry into the ways in which evidence of key events in the development of cancer would make a causal conclusion highly defensible.

We begin with consideration of the term "biologic," which refers (rather arbitrarily) to events occurring within the individual organism; we reserve the terms "behavioral" and "social" to refer to events occurring to individuals or populations, respectively (180). A biologic mechanism, therefore, refers to a series of events within the individual that (from some combination of inherited and acquired factors and processes) produce a malignancy. Our current understanding of the organizational structure of scientific knowledge comprising human cancer biology, however, includes a vast number of explanatory levels that contribute to the mechanism. Put another way (and in the context of smoking and lung cancer), the act of smoking (a socially mediated behavioral phenomenon influenced by the biology of addiction) begins the "biologic mechanism," which can then be described in terms of many different levels of explanation including the physical exposure of epithelial surfaces to smoke, the physical movement of smoke constituents throughout the vascular system, metabolism in tissues and organs, absorption across cellular membranes and throughout

intracellular spaces, and exposure to chromosomes, genes, and nucleic acids. At even deeper levels, there is the formation of DNA-adducts and subsequent alteration in electron and magnetic fields around the atoms making up the DNA molecules. What happens next, after the exposure (i.e., a specific chemical component of smoke or its metabolite) attaches itself to nucleic acid, is typically described in terms of DNA damage, which if not repaired can result in alterations in critical genes, such as tumor suppressor genes and oncogenes. In addition, a host of promoting factors (and competing prevention factors such as micronutrients and phytochemicals) interact with intracellular regulators of cell growth or apoptosis, which determine cell number homeostasis. Dysregulation of these cellular growth and death processes provides the opportunity for the clonal growth of a malignancy from a cell in a tissue in an organ which, eventually, signals to its host that something is amiss through a persistent cough, a dull ache in the chest, or due to an equally complex cascade of behaviorally and socially mediated events, a slight shadow on a radiograph.

Given this systems-oriented structural organization of "ecologic" knowledge (181), what constitutes a biologically plausible mechanism? If by "plausible" we mean "known," as in "fully described at all levels of scientific explanation," then a "known" biologic mechanism is orders of magnitude more complex than what was (inadequately) described in a single paragraph. Thus, the idea that an association is biologically plausible when the mechanism is "known," and sufficient evidence exists to show how the presumed causal factor affects it (30, 37), is too stringent (i.e., over-demanding) to be practically useful. Put another way, with the current lack of understanding of the complexity of cancer biology, no association can be declared plausible using an inferential rule that "each step" in the process, from first exposure to first clinical sign, must be defined.

Any judgment regarding biologic plausibility in the practice of causal inference in epidemiology will be made from evidence collected not only on a subset of the total number of events relevant to the occurrence of cancer, but also on a subset of the levels of explanation involved. Although others in molecular epidemiology have proposed ways to simplify the situation by combining various levels (18), two key concerns remain: at which levels is evidence relatively more important than others, and, at any given level, what is the best (i.e., strongest) type of evidence? In-depth discussions of these issues will require a look at the evolution of methodological technique in molecular and cellular biology and its relation to epidemiologic methodologies.

Conclusion

For that part of the theory and practice of causal inference referred to as "biologic plausibility," progress will likely be made along two broad fronts: by improving the quality of literature reviews such that all biologic hypotheses and accompanying evidence are considered when judgments are made, and by using our expanded understanding of the complex layering of interactive systems that make up the biology of cancer to propose new rules of evidence applicable to the wide range of biologic research results examined in causal assessments.

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REFERENCES

1. Garfinkel L. Perspectives on cancer prevention. *CA* 1995; 45:5-7.
2. Berlin NI. The prevention of cancer—a sobering perspective. *J Clin Epidemiol* 1994;47:573-4.
3. Cole P, Sateren W. The evolving picture of cancer in America. *J Natl Cancer Inst* 1994;87:159-60.
4. Cole P, Amoateng-Adjepong Y. Cancer prevention: accomplishments and prospects. *Am J Public Health* 1994;84:8-10.
5. Shopland DR. Tobacco use and its contribution to early cancer mortality with a special emphasis on cigarette smoking. *Environ Health Perspect* 1995;103(Suppl 8):131-42.
6. Orleans CT. Preventing tobacco-caused cancer: a call to action. *Environ Health Perspect* 1995;103(Suppl 8):149-52.
7. Samet JM. Controlling the avoidable causes of cancer: needs and opportunities for etiologic research. *Environ Health Perspect* 1995;103(Suppl 8):307-11.
8. Susser M. Judgment and causal inference: criteria in epidemiologic studies. *Am J Epidemiol* 1977;105:1-15.
9. Weed DL. Causal and preventive inference. In: Greenwald PG, Kramer BS, Weed DL, eds. *Cancer prevention and control*. New York, NY: Marcel Dekker, 1995:285-302.
10. US Surgeon General's Advisory Committee on smoking and health. US Department of Health, Education, and Welfare, Public Health Service. Washington, DC: US GPO, 1964. (DHHS publication no. (PHS) 1103).
11. Hill AB. The environment and disease: association or causation? *Proc R Soc Med* 1965;58:295-300.
12. Perera FP, Weinstein IB. Molecular epidemiology and carcinogen-DNA adduct formation: new approaches to studies of human cancer causation. *J Chronic Dis* 1982;35: 581-600.
13. Perera FP. Molecular cancer epidemiology: a new tool in cancer prevention. *J Natl Cancer Inst* 1987;78:887-98.
14. Schulte PA. Methodologic issues in the use of biologic markers in epidemiologic research. *Am J Epidemiol* 1987; 126:1006-16.
15. Hulka BS, Wilcosky TC, Griffith JD. *Biological markers in epidemiology*. New York, NY: Oxford University Press, 1990.
16. Hulka BS. Epidemiological studies using biological markers: issues for epidemiologists. *Cancer Epidemiol Biomarkers Prev* 1991;1:13-19.

17. Shields PG, Harris CC. Molecular epidemiology and the genetics of environmental cancer. *JAMA* 1991;266:681-7.
18. Schulte PA, Perera FP. *Molecular epidemiology: principles and practices*. San Diego, CA: Academic Press, 1993.
19. McMichael AJ. Invited commentary—"Molecular epidemiology": new pathway or new traveling companion? *Am J Epidemiol* 1994;140:1-11.
20. Weed DL. Between science and technology: the case of antihistamines and cancer. (Editorial). *J Natl Cancer Inst* 1994;86:740-1.
21. Weed DL. On the use of causal criteria. *Int J Epidemiol* 1997;26:1137-41.
22. Evans AS. *Causation and disease*. New York, NY: Plenum Medical, 1993.
23. Weed DL, Gorelic LS. The practice of causal inference in cancer epidemiology. *Cancer Epidemiol Biomarkers Prev* 1996;5:303-11.
24. Glynn JR. A question of attribution. *Lancet* 1993;342:530-2.
25. Sackett DL. The diagnosis of causation. In: Gent M, Shigematsu I, eds. *Epidemiological issues in reported drug-induced illnesses—SMON and other examples*. Hamilton, Ontario, Canada: McMaster University Library Press, 1978: 106-17.
26. Department of Clinical Epidemiology and Biostatistics, McMaster University Health Sciences Centre. How to read clinical journals. IV. To determine etiology or causation. *Can Med Assoc J* 1981;124:985-90.
27. Rothman KJ. *Modern epidemiology*. Boston, MA: Little Brown, 1986.
28. Susser M. The logic of Sir Karl Popper and the practice of epidemiology. *Am J Epidemiol* 1986;124:711-18.
29. Schlesselman JJ. "Proof" of cause and effect in epidemiological studies: criteria for judgment. *Prev Med* 1987;16: 195-210.
30. Elwood JM. *Causal relationship in medicine: a practical system for critical appraisal*. New York, NY: Oxford University Press, 1988.
31. Gordis L. Challenges to epidemiology in the next decade. *Am J Epidemiol* 1988;128:1-9.
32. Savitz DA. In defense of black box epidemiology. *Epidemiology* 1994;5:550-2.
33. Angell M. The interpretation of epidemiologic studies. *N Engl J Med* 1990;323:823-5.
34. Vandenbroucke JP. Is "the causes of cancer" a miasma theory for the end of the twentieth century? *Int J Epidemiol* 1988;17:708-9.
35. Defining cause. In: Tomatis L, ed. *Cancer: causes, occurrence and control*. Lyon, France: International Agency for Research on Cancer, 1990:97-125. (IARC scientific publication no. 100).
36. Susser M. What is a cause and how do we know one? A grammar for pragmatic epidemiology. *Am J Epidemiol* 1991; 133:635-48.
37. Renton A. Epidemiology and causation: a realist view. *J Epidemiol Community Health* 1994;48:79-85.
38. Skrabanek P. The emptiness of the black box. *Epidemiology* 1994;5:553-5.
39. Weed DL. Epistemology and ethics in epidemiology. In: Coughlin SS, Beauchamp TL, eds. *Ethics and epidemiology*. New York, NY: Oxford University Press, 1996:76-94.
40. Weed DL. Underdetermination and incommensurability in contemporary epidemiology. *Kennedy Inst Ethics J* 1997;7: 107-27.
41. Naguib SKM, Landin FE Jr, Davis HJ. Relation of various epidemiologic factors to cervical cancer as determined by a screening program. *Obstet Gynecol* 1966;28:4551-9.
42. Tokuhata GK. Tobacco and cancer of the genitalia among married women. *Am J Public Health* 1967;57:830-9.
43. Newman G. Early diagnosis of cancer of the cervix—the detection of high-risk patients. *Geburtshilfe Frauenheilkd* 1972;32:574-8.
44. Thomas DB. An epidemiologic study of carcinoma in situ and squamous dysplasia of the uterine cervix. *Am J Epidemiol* 1973;98:10-28.
45. Kessler II, Kulcar Z, Zimolo A, et al. Cervical cancer in Yugoslavia. II. Epidemiologic factors of possible etiologic significance. *J Natl Cancer Inst* 1974;53:51-60.
46. Williams RR, Horn JW. Association of cancer sites with tobacco and alcohol consumption and socioeconomic status of patients: interview study from the Third National Cancer Survey. *J Natl Cancer Inst* 1977;58:525-47.
47. Buckley JD, Harris RWC, Doll R, et al. Case-control study of the husbands of women with dysplasia or carcinoma of the cervix uteri. *Lancet* 1981;2:1010-15.
48. Wigle DT, Mao Y, Grace M. Re: "Smoking and cancer of the uterine cervix: hypothesis." (Letter). *Am J Epidemiol* 1980; 111:125-7.
49. Harris RWC, Brinton LA, Cowdell RH, et al. Characteristics of women with dysplasia or carcinoma in situ of the cervix uteri. *Br J Cancer* 1980;42:359-69.
50. Stellman SD, Austin H, Wynder EL. Cervix cancer and cigarette smoking: a case-control study. *Am J of Epidemiol* 1980;111:383-8.
51. Clarke EA, Morgan RW, Newman AM. Smoking as a risk factor in cancer of the cervix: additional evidence from a case-control study. *Am J Epidemiol* 1982;115:59-66.
52. Lyon JL, Gardner JW, West DW, et al. Smoking and carcinoma in situ of the uterine cervix. *Am J Public Health* 1983;73:558-62.
53. Trevathan E, Layde P, Webster LA, et al. Cigarette smoking and dysplasia and carcinoma in situ of the uterine cervix. *JAMA* 1983;250:499-502.
54. Berggren G, Sjostedt S. Preinvasive carcinoma of the cervix uteri and smoking. *Acta Obstet Gynecol Scand* 1983;62: 593-8.
55. Marshall JR, Graham S, Byers T, et al. Diet and smoking in the epidemiology of cancer of the cervix. *J Natl Cancer Inst* 1983;70:847-51.
56. Hellberg D, Valentin J, Nilsson S. Smoking as a risk factor in cervical neoplasia. (Letter). *Lancet* 1983;2:1497.
57. Martin PMD, Hill GB. Cervical cancer in relation to tobacco and alcohol consumption in Lesotho, Southern Africa. *Cancer Detect Prev* 1984;7:109-14.
58. Vonka V, Kanka J, Hirsch I, et al. Prospective study on the relationship between cervical neoplasia and herpes simplex type-2 virus. II. Herpes simplex type-2 antibody presence in sera taken at enrollment. *Int J Cancer* 1984;33:61-6.
59. Reeves WC, Brinton LA, Brenes MM, et al. Case-control study of cervical cancer in Herrera Province, Republic of Panama. *Int J Cancer* 1985;36:55-60.
60. Mayberry RM. Cigarette smoking, herpes simplex virus type 2 infection, and cervical abnormalities. *Am J Public Health* 1985;75:676-8.
61. Zunzunegui MV, King MC, Coria CF, et al. Male influences on cervical cancer risk. *Am J Epidemiol* 1986;123:302-7.
62. Peters RK, Thomas D, Hagan DG, et al. Risk factors for invasive cervical cancer among Latinas and non-Latinas in Los Angeles County. *J Natl Cancer Inst* 1986;77:1063-77.
63. La Vecchia C, Franceschi S, Decarli A, et al. Cigarette smoking and the risk of cervical neoplasia. *Am J Epidemiol* 1986;123:22-9.
64. Zaninetti P, Franceschi S, Baccolo M, et al. Characteristics of women under 20 with cervical intra-epithelial neoplasia. *Int J Epidemiol* 1986;15:477-81.
65. Baron JA, Byers T, Greenberg ER, et al. Cigarette smoking in women with cancers of the breast and reproductive organs. *J Natl Cancer Inst* 1986;77:677-80.
66. Brinton LA, Schairer C, Haenszel W, et al. Smoking and invasive cervical cancer. *JAMA* 1986;255:3265-9.
67. Brinton LA, Tashima KT, Lehman HF, et al. Epidemiology of cervical cancer by cell type. *Cancer Res* 1987;47: 1706-11.
68. Celentano DD, Klassen AC, Weisman CS, et al. The role of contraceptive use in cervical cancer: the Maryland Cervical

- Cancer Case-Control Study. *Am J Epidemiol* 1987;126:592-604.
69. Reeves WC, Caussy D, Brinton LA, et al. Case-control study of human papillomaviruses and cervical cancer in Latin America. *Int J Cancer* 1987;40:450-4.
 70. Nischan P, Ebeling K, Schindler C. Smoking and invasive cervical cancer risk: results from a case-control study. *Am J Epidemiol* 1988;128:74-7.
 71. Slattery ML, Robison LM, Schuman LK, et al. Cigarette smoking and exposure to passive smoking are risk factors for cervical cancer. *JAMA* 1989;261:1593-8.
 72. Licciardone JC, Wilkins JR III, Brownson RC, et al. Cigarette smoking and alcohol consumption in the aetiology of uterine cervical cancer. *Int J Epidemiol* 1989;18:53-7.
 73. Brisson J, Roy M, Fortier M, et al. Condyloma and intraepithelial neoplasia of the uterine cervix: a case-control study. *Am J Epidemiol* 1988;128:337-42.
 74. Brock KE, MacLennan R, Brinton LA, et al. Smoking and infectious agents and risk of in situ cervical cancer in Sydney, Australia. *Cancer Res* 1989;49:4925-8.
 75. Jones J, Brinton LA, Hamman RF, et al. Risk factors for in situ cervical cancer: results from a case control study. *Cancer Res* 1990;50:3657-62.
 76. Herrero R, Brinton LA, Reeves WC, et al. Invasive cervical cancer and smoking in Latin America. *J Natl Cancer Inst* 1989;81:205-11.
 77. Hirayama T. Operational aspects of cancer public education in Japan. In: Summary Proceedings of the International Conference on Public Education About Cancer. UICC Technical Report Series. Vol 18. Geneva, Switzerland: International Union Against Cancer, 1975:85-90.
 78. Hirayama T. Changing patterns of cancer in Japan with special reference to the decrease in stomach cancer mortality. In: Hiatt HH, Watson JD, Winsten JA, eds. Origins of human cancer. Book A: Incidence of cancer in humans. Cold Spring Harbor Conference on Cell Proliferation. Vol 4. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, 1977:55-75.
 79. Cederlof R, Friberg I, Hrubec Z, et al. The relationship of smoking and some social covariables to mortality and cancer morbidity: a ten year follow-up in a probability sample of 55,000 Swedish subjects ages 18 to 69. Stockholm, Sweden: Department of Environmental Hygiene, The Karolinska Institute, 1975.
 80. Wright NH, Vessey MP, Kenward B, et al. Neoplasia and dysplasia of the cervix uteri and contraception: a possible protective effect of the diaphragm. *Br J Cancer* 1978;38:273-9.
 81. Garfinkel L. Cancer mortality in nonsmokers: prospective study by the American Cancer Society. *J Natl Cancer Inst* 1980;65:1169-73.
 82. Greenberg ER, Vessey M, McPherson K, et al. Cigarette smoking and cancer of the uterine cervix. *Br J Cancer* 1985;51:139-41.
 83. Gram IT, Austin H, Stalsberg H. Cigarette smoking and the incidence of cervical intraepithelial neoplasia, grade III, and cancer of the cervix uteri. *Am J Epidemiol* 1992;135:341-6.
 84. Winkelstein W Jr. Smoking and cancer of the uterine cervix: hypothesis. *Am J Epidemiol* 1977;106:257-9.
 85. Shopland DR. The health consequences of smoking. Cancer: a report of the Surgeon General. US Department of Health and Human Services, Public Health Service, Office on Smoking and Health. Washington, DC: US GPO, 1982; 137-141. (DHHS publication no. (PHS) 82-50179).
 86. Austin DF. Smoking and cervical cancer. *JAMA* 1983;250:516-17.
 87. Winkelstein W Jr, Shillitoe EJ, Brand R, et al. Further comments on cancer of the uterine cervix, smoking, and herpesvirus infection. *Am J Epidemiol* 1984;119:1-8.
 88. Tobacco smoking. In: IARC monograph on the evaluation of the carcinogenic risk of chemicals to humans. Vol 38. Lyon, France: International Agency for Research on Cancer, 1985: 282-92.
 89. Winkelstein W Jr. Cigarette smoking and cancer of the uterine cervix. In: Hoffman D, Harris CC, eds. Mechanisms in tobacco carcinogenesis. Banbury report 23. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, 1986:329-41.
 90. Singer A, Tay SK. Smoking and cervical neoplasia: a serious public health problem. *J Obstet Gynaecol* 1986;6(Suppl 2): S89-90.
 91. Reducing the health consequences of smoking: 25 years of progress. A report of the Surgeon General: 1989 Executive Summary. Rockville, MD: US Department of Health and Human Services, Public Health Service, Centers for Disease Control, Center for Chronic Disease Prevention and Health Promotion, Office of Smoking and Health, 1989:57-8. (DHHS publication no. (CDC) 89-8411).
 92. Layde PM. Smoking and cervical cancer: cause or coincidence? *JAMA* 1989;261:1631-3.
 93. Winkelstein W Jr. Smoking and cervical cancer—current status: a review. *Am J Epidemiol* 1990;131:945-57.
 94. Chamberlain G. Aetiology of gynaecological cancer. *J R Soc Med* 1981;74:246-61.
 95. Brinton LA, Fraumeni JF. Epidemiology of uterine cervical cancer. *J Chronic Dis* 1986;39:1051-65.
 96. Lovejoy NC. Precancerous lesions of the cervix: personal risk factors. *Cancer Nurs* 1987;10:2-14.
 97. McMichael AJ, Hiller JE. Pills, partners and preventive prospects: in-situ cancer of the cervix. *Med J Aust* 1989;150: 114-16.
 98. Einhorn N. Risk factors and etiology in gynecologic cancer. *Curr Opin Oncol* 1990;2:857-63.
 99. Trope CG, Makar AP. Epidemiology, etiology, screening, prevention, and diagnosis in female genital cancer. *Curr Opin Oncol* 1991;3:908-19.
 100. Yoder L, Rubin M. The epidemiology of cervical cancer and its precursors. *Oncol Nurs Forum* 1992;19:485-93.
 101. Graham CA. Cervix cancer prevention and detection update. *Semin Oncol Nurs* 1993;9:155-62.
 102. Shopland DR, Burns DM. Medical and public health implications of tobacco addiction. In: Orleans CT, Slade J, eds. Nicotine addiction: principles and management. New York, NY: Oxford University Press, 1993:105-28.
 103. Daly MB, Bookman MA, Lerman CE. Female reproductive tract: cervix, endometrium, ovary. In: Greenwald P, Kramer BS, Weed DL, eds. Cancer prevention and control. New York, NY: Marcel Dekker, 1995:585-610.
 104. Bornstein J, Rahat MA, Abramovici H. Etiology of cervical cancer: current concepts. *Obstet Gynecol Surv* 1995;50: 146-54.
 105. Shopland DR. Tobacco use and its contribution to early cancer mortality with a special emphasis on cigarette smoking. *Environ Health Perspect* 1995;103(Suppl 8):131-42.
 106. Licciardone JC, Brownson RC, Chang JC, et al. Uterine cervical cancer risk in cigarette smokers: a meta-analytic study. *Am J Prev Med* 1990;6:274-81.
 107. Sood AK. Cigarette smoking and cervical cancer: meta-analysis and critical review of recent studies. *Am J Prev Med* 1991;7:208-13.
 108. Winkelstein W Jr. Smoking and cancer of the cervix. (Letter). *Br J Cancer* 1981;43:736.
 109. Brinton LA. Editorial commentary: smoking and cervical cancer—current status. *Am J Epidemiol* 1990;131:958-60.
 110. Phillips AN, Davey Smith G. Cigarette smoking as a potential cause of cervical cancer: has confounding been controlled? *Int J Epidemiol* 1994;23:42-9.
 111. Petrakis NL, Gruenke LD, Besten TC. Nicotine in breast fluid of nonlactating women. *Science* 1978;199:303-5.
 112. Yamasalis E, Ames BN. Cancer of mutagens from urine by absorption with the nonpolar resin XAD-2: cigarette smokers have mutagenic urine. *Proc Natl Acad Sci U S A* 1977;74: 3555-9.
 113. Petrakis NL, Maack CA, Lee RE, et al. Mutagenic activity in nipple aspirates of human breast fluid. (Letter). *Cancer Res* 1980;40:188-9.

114. Sasson IM, Haley NJ, Hoffmann D, et al. Cigarette smoking and neoplasia of the uterine cervix: smoke constituents in cervical mucus. (Letter). *N Engl J Med* 1985;312:315-16.
115. Ferson M, Edwards A, Lind A, et al. Low natural killer-cell activity and immunoglobulin levels associated with smoking in human subjects. *Int J Cancer* 1979;23:603-9.
116. Holly EA, Petrakis NL, Friend NF, et al. Mutagenic mucus in the cervix of smokers. *J Natl Cancer Inst* 1986;76:983-6.
117. Hellberg D, Nilsson S, Haley NJ, et al. Smoking and cervical intraepithelial neoplasia: nicotine and cotinine in serum and cervical mucus in smokers and nonsmokers. *Am J Obstet Gynecol* 1988;158:910-13.
118. Kreyberg L. Histological lung cancer types: a morphological and biological correlation. *Acta Pathol Microbiol Cancer* 1962;Suppl 152:1-56.
119. Schiffman MH, Haley NJ, Felton JS, et al. Biochemical epidemiology of cervical neoplasia: measuring cigarette smoke constituents in the cervix. *Cancer Res* 1987;47:3886-8.
120. McArdle JP, Muller HK. Quantitative assessment of Langerhans' cells in human cervical intraepithelial neoplasia and wart virus infection. *Am J Obstet Gynecol* 1986;154:509-15.
121. Tay SK, Jenkins D, Maddox P, et al. Subpopulations of Langerhans' cells in cervical neoplasia. *Br J Obstet Gynecol* 1987;94:10-15.
122. Stingl G, Katz SI, Clement L, et al. Immunologic functions of Ia-bearing epidermal Langerhans cells. *J Immunol* 1978;121:2005-13.
123. Barton SE, Jenkins D, Cuzick J, et al. Effect of cigarette smoking on cervical epithelial immunity: a mechanism for neoplastic change? *Lancet* 1988;2:652-4.
124. Jones CJ, Schiffman MH, Kurman R, et al. Elevated nicotine levels in cervical lavages from passive smokers. *Am J Public Health* 1991;81:378-9.
125. Basu J, Mikhail MS, Palan PR, et al. Factors influencing the exfoliation of cervicovaginal epithelial cells. *Am J Obstet Gynecol* 1992;167:1904-9.
126. McCann MF, Irwin DE, Walton LA, et al. Nicotine and cotinine in the cervical mucus of smokers, passive smokers, and nonsmokers. *Cancer Epidemiol Biomarkers Prev* 1992;1:125-9.
127. Holly EA, Cress RD, Ahn DK, et al. Characteristics of women by smoking status in the San Francisco Bay area. *Cancer Epidemiol Biomarkers Prev* 1992;1:491-7.
128. Holly EA, Cress RD, Ahn DK, et al. Detection of mutagens in cervical mucus in smokers and nonsmokers. *Cancer Epidemiol Biomarkers Prev* 1993;2:223-8.
129. Simons AM, Phillips DH, Coleman DV. Damage to DNA in cervical epithelium related to smoking tobacco. *BMJ* 1993;306:1444-8.
130. King MM, Hollingsworth A, Cuzick J, et al. The detection of adducts in human cervix tissue DNA using 32P-postlabelling: a study of the relationship with smoking history and oral contraceptive use. *Carcinogenesis* 1994;15:1097-100.
131. Simons AM, Phillips DH, Coleman DV. DNA adduct assay in cervical epithelium. *Diagn Cytopathol* 1994;10:284-8.
132. Warwick AP, Redman CWE, Jones PW, et al. Progression of cervical intraepithelial neoplasia to cervical cancer: interactions of cytochrome P450 CYP2D6 EM and glutathione s-transferase GSTM1 null genotypes and cigarette smoking. *Br J Cancer* 1994;70:704-8.
133. Goldacre M, Vessey M, Clarke J, et al. Record linkage study of morbidity following vasectomy. In: Lepow IH, Crozier R, eds. *Vasectomy: immunologic and pathophysiologic effects in animals and man*. New York, NY: Academic Press, 1979:567-75.
134. Walker AM, Jick H, Hunter JR, et al. Hospitalization rates in vasectomized men. *JAMA* 1981;245:2315-17.
135. Pettiti DB, Klein R, Kipp H, et al. Vasectomy and the incidence of hospitalized illness. *J Urol* 1983;129:760-2.
136. Massey FJ Jr, Bernstein GS, O'Fallon WM, et al. Vasectomy and health: results from a large cohort study. *JAMA* 1984;252:1023-9.
137. Ross RK, Paganini-Hill A, Henderson BE. The etiology of prostate cancer: what does the epidemiology suggest? *Prostate* 1983;4:333-44.
138. Honda GD, Bernstein L, Ross RK, et al. Vasectomy, cigarette smoking, and age at first sexual intercourse as risk factors for prostate cancer in middle-aged men. *Br J Cancer* 1988;57:326-31.
139. Newell GR, Fueger JJ, Spitz MR, et al. A case-control study of prostate cancer. *Am J Epidemiol* 1989;130:395-8.
140. Sidney S. Vasectomy and the risk of prostatic cancer and benign prostatic hypertrophy. *J Urol* 1987;138:795-7.
141. Rosenberg L, Palmer JR, Zauberman AG, et al. Vasectomy and the risk of prostate cancer. *Am J Epidemiol* 1990;132:1051-5.
142. Mettlin C, Natarajan N, Huben R. Vasectomy and prostate cancer risk. *Am J Epidemiol* 1990;132:1056-61.
143. Guess HA. Invited commentary: vasectomy and prostate cancer. *Am J Epidemiol* 1990;132:1062-5.
144. Howards SS. American Urological Association response to two articles on the relationship of vasectomy and prostate cancer. *Oncology* 1991;5:78-80.
145. Vasectomy and cancer. (Noticeboard). *Lancet* 1991;338:1586.
146. Hayes RB, Pottern LM, Greenberg R, et al. Vasectomy and prostate cancer in US blacks and whites. *Am J Epidemiol* 1993;137:263-9.
147. Rosenberg L, Palmer JR, Zauberman AG, et al. The relation of vasectomy to the risk of cancer. *Am J Epidemiol* 1994;140:431-8.
148. Hsing AW, Wang RT, Gu FL, et al. Vasectomy and prostate cancer risk in China. *Cancer Epidemiol Biomarkers Prev* 1994;3:285-8.
149. John EM, Whittemore AS, Wu AH, et al. Vasectomy and prostate cancer: results from a multiethnic case-control study. *J Natl Cancer Inst* 1995;87:662-9.
150. Zhu K, Stanford JL, Daling JR, et al. Vasectomy and prostate cancer: a case-control study in a health maintenance organization. *Am J Epidemiol* 1996;144:717-22.
151. Sidney S, Quesenberry CP, Sadler MC, et al. Vasectomy and the risk of prostate cancer in a cohort of multiphasic health-checkup examinees: second report. *Cancer Causes Control* 1991;2:113-16.
152. Nienhuis H, Goldacre M, Seagroatt V, et al. Incidence of disease after vasectomy: a record linkage retrospective cohort study. *BMJ* 1992;304:743-6.
153. Giovannucci E, Tosteson TD, Speizer FE, et al. A long-term study of mortality in men who have undergone vasectomy. *N Engl J Med* 1992;326:1392-8.
154. Giovannucci E, Ascherio A, Rimm EB, et al. A prospective cohort study of vasectomy and prostate cancer in US men. *JAMA* 1993;269:873-7.
155. Giovannucci E, Tosteson TD, Speizer FE, et al. A retrospective cohort study of vasectomy and prostate cancer in US men. *JAMA* 1993;269:878-82.
156. Hiatt RA, Armstrong MA, Klatsky AL, et al. Alcohol consumption, smoking and other risk factors and prostate cancer in a large health plan cohort in California (United States). *Cancer Causes Control* 1994;5:66-72.
157. Moller H, Knudsen LB, Lynge E. Risk of testicular cancer after vasectomy: cohort study of over 73,000 men. *BMJ* 1994;309:295-9.
158. DerSimonian R, Clemens J, Spirtas R, et al. Vasectomy and prostate cancer risk: methodological review of the evidence. *J Clin Epidemiol* 1993;46:163-72.
159. Skegg DCG. Vasectomy and risk of cancers of prostate and testis. *Eur J Cancer* 1993;29A:935-6.
160. Boyle P, Zardize DG. Risk factors for prostate and testicular cancer. *Eur J Cancer* 1993;29A:1048-55.

161. Howards SS. Possible biological mechanisms for a relationship between vasectomy and prostatic cancer. *Eur J Cancer* 1993;29A:1060-2.
162. Pienta KJ, Esper PS. Risk factors for prostate cancer. *Ann Intern Med* 1993;118:793-803.
163. AVSC technical statement: vasectomy and prostate cancer. Washington, DC: Association for Voluntary Surgical Contraception, 17 February, 1993.
164. NICHD, NCI, NIDDK final statement—Vasectomy and Prostate Cancer Conference. Bethesda, MD: National Institute of Child Health and Human Development, National Cancer Institute, National Institute of Diabetes and Digestive and Kidney Diseases, March 2, 1993.
165. Raspa RF. Complications of vasectomy. *Am Fam Physician* 1993;48:1264-8.
166. Klitsch M. Vasectomy and prostate cancer: more questions than answers. *Fam Plann Perspect* 1993;25:133-5.
167. Howards SS, Peterson HB. Vasectomy and prostate cancer: chance, bias, or a causal relationship? (Editorial). *JAMA* 1993;269:913-14.
168. Farley TMM, Meirik O, Mehta S, et al. The safety of vasectomy: recent concerns. *Bull World Health Organ* 1993;71:413-19.
169. Healy B. Does vasectomy cause prostate cancer? *JAMA* 1993;269:2620.
170. Guess HA. Is vasectomy a risk factor for prostate cancer? *Eur J Cancer* 1993;9A:1055-60.
171. Skegg D. Vasectomy and prostate cancer: is there a link? *N Z Med J* 1993;106:242-3.
172. Pollack AE. Vasectomy and prostate cancer. *Adv Contracept* 1993;9:181-6.
173. Howards SS. Vasectomy and prostate cancer. *West J Med* 1994;160:166-7.
174. Wildschut HJ, Monincx W. Vasectomy and the risk of prostate cancer. (Point of View). *Bull World Health Organ* 1994;72:777-8.
175. Tripathy SP, Ramachandran CR, Ramachandran P. Health consequences of vasectomy in India. *Bull World Health Organ* 1994;72:779-82.
176. Hayes RB. Are dietary fat and vasectomy risk factors for prostate cancer? *J Natl Cancer Inst* 1995;87:629-30.
177. Key T. Risk factors for prostate cancer. In: *Cancer surveys. Preventing prostate cancer: screening versus chemoprevention*. Vol 23. Oxford, England: Imperial Cancer Research Fund, 1995:63-77.
178. Weed DL. Methodologic guidelines for review papers. *J Natl Cancer Inst* 1997;89:6-7.
179. Weed DL. Meta-analysis under the microscope. *J Natl Cancer Inst* 1997;89:904-5.
180. Weed DL. The behavior biology interface in cancer prevention and control. *Prev Med* 1997;26:S37-41.
181. Susser M, Susser E. Choosing a future for epidemiology. II. From black box to Chinese boxes and eco-epidemiology. *Am J Public Health* 1996;86:674-7.

Exhibit 29

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Formaldehyde as a Potential Human Leukemogen: An Assessment of Biological Plausibility

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The International Agency for Research on Cancer (IARC, 2004) recently reevaluated the epidemiological data on formaldehyde and concluded that there was “strong but not sufficient evidence for a causal association between leukaemia and occupational exposure to formaldehyde.” This conclusion was tempered since a mechanism for leukemia induction could not be identified. Chemically induced leukemia is a well-studied phenomenon with benzene and a number of cancer chemotherapeutic drugs recognized as capable of causing this effect. Abundant in vitro and in vivo data in animals and humans demonstrate that exposure to sufficient doses of these recognized leukemogens can initiate a cascade of events leading to hematopoietic toxicity and the subsequent development of leukemia. This review addresses the biological plausibility that formaldehyde might be capable of causing any type of leukemia by providing a broad overview of the scientific data that must be considered in order to support or refute a conclusion that a particular substance might be leukemogenic. Data on benzene and selected chemotherapeutic cancer drugs are used as examples and are briefly summarized to demonstrate the similar biological events thought to result in leukemogenesis. These data are compared and contrasted with the available data on formaldehyde in order to judge whether they fulfill the criteria of biological plausibility that formaldehyde would be capable of inducing leukemia as suggested by the epidemiological data. Based on the epidemiological data, it is reasonable to expect that if formaldehyde was capable of inducing leukemia, in vivo and in vitro data would offer supporting evidence for biological plausibility. In particular, there is (1) no evidence to suggest that formaldehyde reaches any target organ beyond the site of administration including the bone marrow, (2) no indication that formaldehyde is toxic to the bone marrow/hematopoietic system in in vivo or in vitro studies, and (3) no credible evidence that formaldehyde induces leukemia in experimental animals. As discussed in this review, based on the key biological events that occur in the process of chemically induced leukemia, there is inadequate biological evidence currently available to corroborate existing weak epidemiological associations. This provides an insufficient database to conclude that there is a causal relationship for formaldehyde and leukemia risk.

Keywords Biological Plausibility, Formaldehyde, Leukemia, Leukemogenesis, Mode of Action

I. INTRODUCTION

The International Agency for Research on Cancer (IARC, 2004) recently reevaluated formaldehyde and concluded that two recent studies provided “strong but not sufficient evidence

for a causal association between leukaemia and occupational exposure to formaldehyde.” The conclusion reached by IARC was based primarily on the observation that “the Working Group could not identify a mechanism for leukaemia induction, and this tempered their interpretation of the epidemiological evidence.”

IARC (2004) also concluded that the previously discounted leukemia results reported in seven studies of embalmers, funeral-parlor workers, pathologists, and anatomists, were now

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supported by the results of two studies of U.S. industrial workers (i.e., Hauptmann et al., 2003, and Pinkerton et al., 2004). While these epidemiological data form the basis for the “strong but not sufficient” conclusion by IARC (2004), a critical weight-of-evidence evaluation of the epidemiological literature is beyond the scope of this review. However, the results of the most recent studies as well as several critiques of these findings are summarized in the next section.

In order to assess the likelihood that formaldehyde might be leukemogenic, it is necessary to consider the biological basis for leukemogenesis as it is presently understood. That is, what is the biological evidence necessary to conclude that a particular chemical substance is capable of inducing leukemia in either animals or humans? Chemically induced leukemia is a well-studied phenomenon with numerous chemicals demonstrating this capability. For example, abundant *in vitro* and *in vivo* data in animals and humans demonstrate that exposure to sufficient doses of benzene can initiate a cascade of events leading to hematopoietic toxicity and the subsequent development of acute myelogenous leukemia (AML). The mechanism(s) responsible for benzene-induced leukemia are not completely understood; however, it has been established that several benzene metabolites may be responsible for bone marrow toxicity (Snyder and Hedii, 1996; Medinsky et al., 1996; Snyder, 2000). The pathway to hematotoxicity and leukemia involves a continuum of events including the likelihood of clastogenic effects from benzene metabolites, perturbations of specific metabolic and detoxification enzymes leading to increased sensitivity or susceptibility of precursor hematopoietic stem cells, and finally interference with regulatory proteins responsible for normal hematopoiesis (U.S. EPA/NCEA, 1997, ATSDR, 1999; Snyder, 2000).

Other chemicals and exposures have also been associated with the induction of leukemia in humans and animals. These include a number of alkylating agents (i.e., cyclophosphamide, chlorambucil, Myleran), topoisomerase inhibitors (i.e., etoposide, teniposide and doxorubicin), and ionizing radiation. All of these leukemogenic exposures exert documented bone marrow toxicity and also demonstrate a range of positive effects in a variety of *in vitro* tests for hematopoietic toxicity. In other words, all of these substances or exposures share a commonality of biological plausibility as support for their demonstrated leukemogenic properties. A comprehensive review by the U.S. Environmental Protection Agency (EPA) of chemical and radiation-induced leukemogenesis in humans and rodents of many of the same chemicals as considered in the present review (with the notable exception of formaldehyde) confirms the necessity of a general sequence of biological events (U.S. EPA/NCEA, 1997).

IARC (2004) was unable to identify a specific mechanism for leukemia induction as a consequence of exposure to formaldehyde. The lack of corroborating mechanistic data renders the interpretation of the epidemiological evidence somewhat equivocal. Attempting to identify a biologically plausible mode of action would result in one of two likely outcomes:

- A demonstration of biological plausibility for leukemogenesis as a consequence of exposure to formaldehyde would offer compelling and corroborative support for the epidemiological findings.
- A demonstration that it is biologically implausible that leukemia can be caused by formaldehyde would suggest that the epidemiological findings were either incorrect, confounded, or spurious.

Consequently, a critical review of the biological plausibility that formaldehyde might be capable of causing leukemia is likely to either support or refute the epidemiological findings. This review is intended to provide a broad overview of the scientific data that must be considered in order to support or reject a conclusion that a particular substance might be capable of inducing leukemia. Data on benzene and selected chemotherapeutic cancer drugs are used as examples and summarized with enough detail to demonstrate the general consistency of biological events leading to leukemogenesis. These data are then compared and contrasted with the available data on formaldehyde in order to judge whether they fulfill the criteria of biological plausibility that formaldehyde would be capable of inducing leukemia as suggested by the epidemiological data. The comparative approach as just outlined was taken, rather than a formal weight-of-evidence analysis using mode-of-action data as detailed in the U.S. EPA recently revised cancer risk assessment guidelines (U.S. EPA, 2005). These guidelines lay out a detailed framework for establishing the mode of action of an individual chemical. As described later, given the lack of any experimental data suggesting that formaldehyde might have leukemogenic properties, the only way to assess these data in the context of leukemogenesis was in comparison with the mode of action of known leukemogenic substances.

II. OVERVIEW OF RECENT EPIDEMIOLOGICAL FINDINGS AND CRITIQUES CONCERNING REPORTED ASSOCIATION BETWEEN FORMALDEHYDE AND LEUKEMIA

The study by Hauptmann et al. (2003) consisted of a cohort of 25,619 industrial workers at 10 U.S. industrial plants where formaldehyde was either produced, or used in the production of other products. Formaldehyde exposure was assessed by peak, average intensity, cumulative, and duration. Compared with workers exposed to low peak levels of formaldehyde (0.1–1.9 ppm), relative risks for leukemia (particularly myeloid leukemia) were 2.43 (95% CI = 0.81–7.25) and 3.46 (95% CI = 1.27–9.43) for workers exposed to peak levels of 2.0–3.9 ppm and ≥ 4.0 ppm, respectively. Compared with workers exposed to low levels of average exposure intensity of formaldehyde (0.1–0.4 ppm), workers exposed to 0.5–0.9 ppm and ≥ 1.0 ppm average intensity had relative risks of 1.15 (95% CI = 0.41–3.23) and 2.49 (95% CI = 1.03–6.03), respectively. The relative risk for leukemia was not significantly associated with cumulative exposure or with duration of exposure.

Using the original data from Hauptmann et al. (2003), this cohort has been reanalyzed by Marsh and Youk (2004). The U.S. and local county rate-based standardized mortality ratios (SMRs) and relative risks (RR) of leukemia and myeloid leukemia (ML) were recomputed by the same four categories of formaldehyde exposure metrics as used by Hauptmann et al. (2003), in addition to an alternative categorization based on tertiles of deaths from all leukemia among exposed subjects. This analysis revealed that the elevated RR for all types of leukemia combined and for ML RRs and associated trends reported by Hauptmann et al. (2003) for highest peak and average intensity of formaldehyde exposure categories occurred because null (or slight) to moderate mortality excesses were compared with statistically significant baseline deficits in deaths from these diseases in the internal comparison group. The alternative categorization based on average intensity of exposure yielded leukemia and ML SMRs close to 1.0 in the highest exposure category, and also demonstrated less evidence of a trend in RRs for leukemia and ML. Similar to the findings of Hauptmann et al. (2003), there was no association for cumulative and duration of formaldehyde exposure as well as no consistent evidence that leukemia or ML risks increased with increasing duration of time spent in a given highest peak exposure. This reanalysis, therefore, did not support the conclusions reached by Hauptmann et al. (2003) that a causal association between formaldehyde exposure and increased mortality from leukemia and ML exists.

In the study by Pinkerton et al. (2004), the mortality experience of 11,039 garment workers exposed to formaldehyde for 3 months or more at three plants was evaluated. While noting that the mean time-weighted average formaldehyde exposure at the three plants in the early 1980s was 0.15 ppm and that past exposures may have been substantially higher, no individual formaldehyde exposure measurements were available. Compared to U.S. mortality rates, in the total cohort, mortality from myeloid leukemia was not significantly increased (SMR = 1.44, 95% CI 0.80–2.37). Mortality from myeloid leukemia was greatest among workers first exposed in the earliest years, when exposures were presumably higher. Among workers with both 10 years or more of exposure and 20 years or more since first exposure, mortality from leukemia and myeloid leukemia were significantly increased (SMR = 1.92, 95% CI 1.08–3.17) and (SMR = 2.55, 95% CI 1.10–5.03), respectively.

In another recent study of a cohort of 14,014 men employed after 1937 at six British factories where formaldehyde was produced or used, there was no increased mortality from leukemia relative to the national population even in those exposed at 2 ppm or greater (SMR = 0.71, 95% CI 0.31–1.39) (Coggon et al., 2003).

In a letter to the editor, Casanova et al. (2004) raised the issue of the lower than expected mortality from lymphohematopoietic disease (SMR = 0.6, 95% CI 0.4–0.7) and leukemia (SMR = 0.5, 95% CI 0.28–0.8) in the referent group (<2 ppm) as the basis for the findings of Hauptmann et al. (2003). Also noted was the lack of a significant association with all lymphohematopoi-

etic neoplasms in formaldehyde-exposed workers in comparison with an external comparison group (SMR = 0.8, 95% CI 0.7–0.9). In response, Hauptmann et al. (2004) disagreed that external comparisons were appropriate and that other workers were the preferred comparison group, although they did not directly address the consequences of a deficit in lymphohematopoietic neoplasms in the internal comparison group. They also reiterated that the increasing risk with increasing exposure as originally reported was an important element in support of an exposure-response relationship.

Cole and Axten (2004) have also critically evaluated the epidemiological data supporting the conclusion that a causal association between leukemia and exposure to formaldehyde exists. This review considered the recent studies by Hauptmann et al. (2003), Coggon et al. (2003), and Pinkerton et al. (2004), as well as previous studies in the context of the established causation criteria, that is, consistency, strength of association, coherence, dose-response, and biological plausibility. The authors concluded, "In sum, then, the formaldehyde-leukemia hypothesis fails each of the four guidelines of general causation. This is hardly surprising in view of the weak and inconsistent findings in the most recent epidemiologic research and the consistent findings in animal studies."

As described earlier, particularly the results of the Hauptmann et al. (2003) study on increased mortality risks from leukemia in the large National Cancer Institute (NCI) formaldehyde cohort study have generated controversy pertaining to the validity of the reported findings. Because these studies are complicated, there are legitimate grounds for differences of opinion on how the data are interpreted. However, the consistency of the skepticism is noteworthy. Even though the NCI study was published in 2004, NCI has already agreed to undertake an update of their study, which will add an additional 8 years of already available data to the evidence. This update should confirm or refute whether exposure to formaldehyde is associated with increased risk of cancer.

III. BENZENE

Benzene was first identified as a human carcinogen as a consequence of a clear causal association between occupational exposure and the development of acute myelogenous leukemia (AML) in humans following long-term exposure (Aksoy, 1989; Infante et al., 1977; NTP 1994; IARC, 1987). Paradoxically, however, despite abundant animal data confirming the carcinogenicity of benzene (e.g., Zymbal gland carcinoma, skin, lymphoma, mammary carcinoma, etc.) (e.g., Huff et al., 1989), early studies with benzene were unable to confirm its leukemogenic properties as observed in humans. Cronkite et al. (1984) reported a highly significant increase in thymic and non-thymic lymphomas in C57BL/6 mice exposed to 300 ppm of benzene by inhalation 6 h/day, 5 days/week for 16 weeks. In a continuation of that study (Cronkite et al., 1985), a definite pattern for thymic and nonthymic lymphoma appearance and mortality was observed. While the underlying reasons are

not clear, lymphomas/lymphatic leukemias are the predominant form of benzene-induced hematological neoplasia in rodents. Clear species specificity exists between rodents and humans, as acute myeloid leukemia is the only malignancy associated with benzene exposure in humans.

Several additional studies have shown benzene to be leukemogenic in rodents following inhalation exposure, thereby providing an animal model for more detailed study of potential modes of action. In a study by Snyder et al. (1984), Sprague-Dawley rats exposed to 100 ppm benzene for 6 h/day, 5 days/week for a lifetime developed myelogenous leukemia and liver tumors. In a series of studies (Cronkite, 1986; Cronkite et al., 1984, 1985), C57BL/6 and CBA/Ca mice were exposed to 300 ppm benzene by inhalation 6 h/day, 5 days/week for 16 weeks. These mouse strains were used because of their susceptibilities to ionizing radiation-induced thymic lymphoma and also for their low spontaneous rates of AML. CBA/Ca male mice exposed to 100 ppm of benzene 6 h/day, 5 days/week for 16 weeks developed myelogenous leukemia, while C57BL/6 mice similarly exposed to 300 ppm had a significant increase in the incidence of thymic and nonthymic lymphomas (Cronkite, 1986; Cronkite et al., 1989). Increased incidences of Harderian and Zymbal gland, squamous-cell, and mammary carcinoma, papilloma, and adenocarcinoma of lungs were also seen. The responses of rodents and humans to chronic benzene exposure are not the same particularly with regard to leukemia induction. Nonetheless, myeloproliferative disorders following benzene exposure in rodents have been used with varying degrees of success to investigate benzene-induced leukemia.

Studying the influence of benzene on the hematopoietic system in rodents has provided some useful insights into the potential mode of action. In female BDF₁ mice, benzene inhalation exposure at 100, 300, and 900 ppm for 6 h/day, 5 days/week for 8 weeks produced pronounced effects on erythroid committed bone marrow progenitor cells as measured by various *in vitro* culture assays (erythroid burst-forming unit [BFU-E] and erythroid colony-forming unit [CFU-E] assays; Seidel et al., 1989). Farris et al. (1997) conducted an inhalation study in male B6C3F1 mice exposed to 1, 5, 10, 100, and 200 ppm benzene for 6 h/day, 5 days/week for 1, 2, 4, or 8 weeks. While there were no significant effects on hematopoietic parameters below 10 ppm, 100 and 200 ppm reduced the number of total bone marrow cells, progenitor cells, differentiating hematopoietic cells, and most peripheral blood parameters. In addition, replication of bone-marrow-derived hematopoietic progenitor (HPC) cells was increased during the exposure period as likely compensation for the cytotoxicity induced by 100 and 200 ppm benzene. In a similar study, male B6C3F1 mice were exposed to 0, 1, 10, 100, or 200 ppm benzene by inhalation for 6 h/day, 5 days/week, for 1, 2, 4, or 8 weeks, with evaluations of primitive and committed progenitor cells, differentiating and maturing lineage-specific cells, and stromal cells in the bone marrow at each sampling time. At 100 and 200 ppm there were rapid and significant reductions in number of reticulocytes in the blood, B lymphocytes

in the bone marrow and spleen, and an increased frequency of micronucleated reticulocytes in the bone marrow, thus demonstrating substantial hematopoietic toxicity (Farris et al., 1996).

In an *in vivo/in vitro* study, mice were exposed to 300 ppm benzene for 6 h/day, 5 days/week for 2 weeks, followed by growth of bone marrow cells grown in long-term bone marrow culture. Bone marrow cultures initiated 1 day after the last benzene exposure did not produce adequate numbers of hematopoietic cells over 3 weeks, and, in most cases, no erythroid or myeloid clonogenic were recovered. These results clearly demonstrate the bone marrow target organ specificity of benzene exposure (Abraham, 1996). Numerous other *in vivo* and *in vitro* studies attest to the effects of benzene on bone-marrow-derived hematopoietic stem and progenitor cell differentiation (Irons and Stillman, 1996b; Niculescu and Kalf, 1995) and gene expression profiles in bone marrow and hematopoietic stem cells (Faiola et al., 2004). In addition, several hypotheses regarding potential modes of leukemogenic action of benzene have been published, including cell cycle suppression in hematopoietic progenitor and stem cells and selective chromosomal aberrations in bone marrow cells (Yoon et al., 2001; Hsieh et al., 1999; Stillman et al., 2000; Irons and Stillman, 1996a; Parke, 1996; Snyder and Hedii, 1996). Consequently, it is reasonable to conclude that leukemogenic transformation induced by benzene involves damage to the bone marrow and a resulting dysregulation of hematopoiesis.

IV. CANCER CHEMOTHERAPEUTIC DRUGS AND OTHER EXPOSURES AS LEUKEMOGENIC SUBSTANCES

A. Alkylating Agents

It has been generally recognized that treatment of primary malignancies with cytotoxic drugs that act as alkylating agents can lead to myelodysplastic syndrome (MDS) and/or acute myelogenous leukemia (Jandl, 1997). This list includes, but is not limited to, melphalan, chlorambucil, busulfan, cyclophosphamide, and nitrosourea (IARC, 1987). Since most modern therapeutic regimens utilize a combination of drugs, it is often difficult to discern the precise offending agent. Nonetheless, as a class, there can be little doubt that treatment with these drugs alone or in various chemical “cocktails” increases the risk of developing secondary AML (s-AML). Secondary leukemias have been estimated to account for 10–30% of all AML (Leone, 1999). The exact risk is not known with certainty and will likely vary considerably depending on treatment and primary disease (Pui, 1991; Pedersen-Bjergaard, 1985; Brusamolina, 1998).

It is also clear that AML arising secondary to treatment with alkylating chemotherapeutic agents often possesses morphological and cytogenetic characteristics that can be used to distinguish it from AML arising *de novo*, or primary, which has no readily identifiable cause in most patients (Coltman and Dahlberg, 1990; Park and Koeffler, 1996). This includes disease progression and the presence of specific cytogenetic

abnormalities (Jandl, 1997; Leone et al., 1999; Pedersen-Bjergaard et al., 1985, 2002). As the disease progresses, cytogenetic abnormalities are observed in virtually every case of s-AML, providing evidence of the genotoxic mechanism involved in the origin of the disease (Jandl, 1997; Leone et al., 1999; Linet et al., 1996; Snyder and Kalf, 1994).

All of the cytotoxic alkylating chemotherapeutic drugs that cause s-AML display damaging effects on the bone marrow. Because bone marrow is an organ with rapid cell growth, the hematopoietic toxicity of cytotoxic agents is a consequence of the very property for which they are used clinically, that is, to kill rapidly growing cancer cells. Confirmatory of their leukemogenic potential, numerous epidemiological studies of patients receiving a variety of such drugs have shown associations with leukemia in addition to other types of cancer (e.g., bladder cancer). For many of these drugs, their leukemogenic potential has also been confirmed in experimental animal studies, as well as in *in vitro* studies demonstrating bone marrow toxicity. While it is beyond the scope of this review to consider in detail the volume of data on this complex issue, some of the relevant data on a few cancer chemotherapeutic drugs associated with leukemia are described in order to illustrate the point that their potential to cause leukemia in humans is supported by concordant *in vivo* and/or *in vitro* data showing a similar potential. However, unlike the extensive database for benzene, including detailed studies on a likely mode of action, the animal data for these cancer chemotherapeutic drugs are far less robust. Nevertheless, these data reinforce the idea that to conclude that it is biologically plausible that any particular substance might be capable of causing leukemia requires that certain basic criteria be satisfied (U.S. EPA/NCEA, 1997).

It should be noted that x-ray and γ radiation also unequivocally cause leukemia in animals and humans, and also demonstrate considerable bone marrow/hematopoietic toxicity in both *in vivo* and *in vitro* systems (IARC, 2000; U.S. EPA/NCEA, 1997). However, these exposures are not included in this review due to the fact that unlike chemicals, which must be absorbed and distributed via the circulation to the bone marrow in order to induce leukemogenic effects, radiation-induced leukemogenesis with penetration through the body does not involve this critical step.

1. Cyclophosphamide

Cyclophosphamide is probably the most studied of the cancer chemotherapeutic drugs with an established ability to cause secondary human leukemia (IARC, 1987). For example, among 602 patients treated predominantly with cyclophosphamide for non-Hodgkin's lymphoma in Denmark, 9 cases of acute non-lymphocytic leukemia (ANLL) or preleukemia (i.e., MDS) were observed, compared to 0.12 expected on the basis of incidence rates in the general population (Pedersen-Bjergaard et al., 1985). The finding of preleukemia (i.e., MDS) is highly indicative of frank bone marrow insult. In the United States, 3 three cases of

ANLL or preleukemia were observed among 333 women treated only with cyclophosphamide for ovarian cancer, while 1.2 cases were expected (Greene et al., 1986). In Germany, a case-control study of leukemia arising as a second primary malignancy following breast or ovarian cancer was reported by Haas et al. (1987). Relative risks of 1.5, 3.3, and 7.3 were estimated in association with cumulative doses of <10 g, 10–29 g, and >30 g cyclophosphamide, respectively.

In numerous short-term *in vivo* assays in mice, cyclophosphamide demonstrates substantial dose-related effects on pluripotent and committed stem-cell colony-forming-unit assays (CFU-S and CFU-C). Similar effects have also been reported in assays conducted with human stem cells. Some of these effects have been reversible after cessation of dosing. Repeated or chronic administration of cyclophosphamide has also produced various dose-related adverse effects on hematopoietic stem cells. In humans, clinical administration of cyclophosphamide has produced severe depression of peripheral white blood cells (WBC), that is, pancytopenia. Doses had to be reduced or discontinued after more than 4 months due to increasing sensitivity of the granulopoietic system to the drug, suggesting cumulative toxicity (Lohrmann and Schreml, 1982).

Lifetime oral administration of low doses of cyclophosphamide to Sprague-Dawley rats produced malignant tumors in lymphoid and hematopoietic tissues, in addition to other organs (Schmahl and Habs, 1978). Doses were administered 5 days/week in drinking water. Of interest was the finding that while the highest dose (2.5 mg/kg/day) produced a clear carcinogenic effect in hematopoietic tissue over controls, lower doses (0.31–1.25 mg/kg/day) produced a greater effect. In a study designed to investigate the extent to which the induction of leukemia by cyclophosphamide might be influenced by genetic predisposition, this drug was administered *sc* at 13 and 26 mg/kg weekly for a lifetime to AKR mice, which are genetically predisposed to develop leukemias, and to NMRI mice, which exhibit a low spontaneous leukemia rate. In AKR mice, cyclophosphamide decreased the incidence of leukemias by 17% and 37%, respectively, while in NMRI mice, cyclophosphamide significantly increased the incidence of leukemias by 46% at the low dose and 26% at the high dose (Petru et al., 1989). The effects of daily *sc* administration of cyclophosphamide to female NZB/NZW mice at 1 or 8 mg/kg was reported by Walker and Bole (1971). Six of 10 high-dose animals developed leukemias and other malignancies after 36 to 64 weeks of treatment. These findings support the leukemogenic potential of cyclophosphamide.

Genotoxicity data in humans have demonstrated increased incidence of sister chromatid exchanges in peripheral blood lymphocytes and, in one study, in bone marrow cells of patients treated with cyclophosphamide for a variety of malignant and nonmalignant diseases (IARC, 1987). While consistently positive results have also been reported when cyclophosphamide has been tested for genetic effects in a wide variety of *in vivo*

and in vitro tests, all of these findings are nonspecific and not confirmatory of leukemogenic potential.

The totality of the data on cyclophosphamide indicates that it is a carcinogen with the bone marrow as one of its primary target organs. This is evidenced by the induction of leukemia in both animals and humans as well as multiple in vitro short-term and in vivo chronic studies. Taken collectively, these data support clinical evidence for its leukemogenic potential.

2. *1,4-Butanediol Dimethanesulfonate (Myleran)*

According to the IARC (1987), there is sufficient evidence to conclude that Myleran is carcinogenic in humans. In a study of 69 patients with bronchial carcinoma who had been treated with Myleran and survived for 5 years, 4 developed acute non-lymphocytic leukemia (3 myelomonocytic leukemias and 1 erythrocytopenia) and 15 others developed, pancytopenia in the succeeding 4 years. In contrast, among 148 other survivors at 5 years who had not been given Myleran, 1 case of pancytopenia was reported (Stott et al., 1976). Stott et al. (1976) reported the 5-year findings of a double-blind study following long-term chemotherapy with Myleran or cyclophosphamide for carcinoma of the bronchus compared with a group receiving a placebo. Hematological toxicity, especially thrombocytopenia, was frequent and severe in the patients who were treated with Myleran, and low platelet counts continued long after chemotherapy was discontinued.

In animals, Myleran has been tested for carcinogenicity by intraperitoneal (ip) injection and by intravenous (iv) injection in mice and rats and by oral administration to rats with both positive and negative findings. Administration of Myleran to mice (ip) did not increase the incidence of tumors in two studies (IARC, 1974; Stoner et al., 1973). However, leukemia and hypoplastic bone marrow were reported in two other studies (Chu et al., 1981; Morley and Blake, 1974).

In numerous short-term in vivo assays in mice, Myleran demonstrates substantial doserelated effects on hematopoietic proliferation and differentiation (CFU-S and CFU-C assays). Similar effects have also been reported in assays conducted in dogs with a dose-dependent reduction of CFU-C. These effects have generally been reversible after cessation of dosing, although, depending on the dose and particular assay, recovery may be slow. Repeated or chronic administration of Myleran has also produced various dose-related adverse effects on hematopoietic progenitor cells, with the most prominent effects on the least mature cells among hematopoietic progenitor cells. Additional studies suggest that hematopoietic failure may be a consequence following sufficient doses of Myleran, which produces a long-term inability of stromal cells to reproduce and support normal hematopoiesis (Lohrmann and Schreml, 1982; Guest and Uetrecht, 2000; Trainor and Morley, 1976; Dunn and Elson, 1970).

Chronic treatment of rodents with Myleran in vivo induced dominant lethal mutations and increased the frequency

of chromosomal aberrations and micronuclei in bone marrow cells; in single studies, Myleran induced DNA damage but not mutation. Myleran is genotoxic, as shown by its ability to induce chromosomal aberrations and sister chromatid exchanges in human and rodent cells in vitro and mutation in rodent cells in vitro (IARC, 1987), although these findings are nonspecific and not confirmatory of leukemogenic potential.

The totality of the data on Myleran indicates that it is a carcinogen with the bone marrow as one of its primary target organs. This is evidenced by the induction of leukemia in both animals and humans as well as multiple in vitro short-term and in vivo chronic studies. Taken collectively, these data support clinical evidence for its leukemogenic potential.

3. *Chlorambucil*

According to the IARC (1987), there is sufficient evidence to conclude that chlorambucil is carcinogenic in humans. Chlorambucil is an alkylating chemotherapeutic drug used for the treatment of cancer (i.e., breast and ovarian) as well as other non-cancer diseases such as juvenile arthritis and glomerulonephritis. While the studies demonstrating the carcinogenicity of chlorambucil are small and in some cases involve simultaneous exposure to radiation or other potential carcinogens, all report an excess of subsequent malignancy, particularly acute nonlymphocytic leukemia (ANLL) (IARC, 1981; Green et al., 1982). Berk et al. (1981) reported a 13-fold increase in the incidence of ANLL in 431 polycythemia vera patients receiving chlorambucil therapy. The incidence of ANLL was 2.3 times higher than in patients receiving radioactive phosphorus, with the excess strongly related to the dose of chlorambucil. Reimer et al. (1977) reported on acute leukemia following the use of a variety of alkylating agents (e.g., cyclophosphamide, chlorambucil, etc.) for the treatment of ovarian cancer. Thirteen cases of ANLL occurred among 5455 patients compared to 0.62 cases expected (RR = 21.09). Similar long-term follow-up studies of patients treated for a variety of cancers with alkylating agents have also reported increased incidence of leukemia (Petru and Schmahl, 1991).

In animals, chlorambucil has been tested for carcinogenicity in mice and rats by ip injection and in female rats by oral gavage. It produced tumors of the lung, hematopoietic system and ovaries in mice (IARC, 1981), and hematopoietic tumors in male rats and hematopoietic and lymphatic tumors in female rats (IARC, 1981; Berger et al., 1985; Weisburger, 1977).

Chlorambucil also produces residual bone marrow toxicity in mice following exposure as measured by CFU-S, CFU-C, and significant reductions in tibial bone marrow cellularity (Trainor et al., 1979; Van Putten and Lelieveld, 1971). Valeriote and Tolen (1972) reported decreased survival of hematopoietic colony-forming cells in vivo following administration of chlorambucil. Chlorambucil is genotoxic, as demonstrated by its ability to induce sister chromatid exchanges and chromosomal aberrations in human lymphocytes, sister chromatid exchanges and mutation in Chinese hamster cells in vitro and mutations in bacterial test

systems (IARC, 1987), although these findings are nonspecific and not confirmatory of leukemogenic potential.

The totality of the data on chlorambucil demonstrates that it is a carcinogen with the bone marrow as one of its primary target organs, as evidenced by the induction of leukemia in both animals and humans. In vivo studies also demonstrate that the hematopoietic system (i.e., bone marrow) is a target organ for chlorambucil-induced adverse effects, thus confirming its leukemogenic potential.

B. Topoisomerase Inhibitors

Recently, clinical studies have revealed that a different form of AML can arise secondary to treatment with drugs that primarily target topoisomerase II, an enzyme required for DNA replication, recombination, and repair (Beaumont et al., 2003; Hoffman et al., 1995; Anderson et al., 2002; De Renzo et al., 1999; Pedersen-Bjergaard et al., 2002). Etoposide, teniposide, and other epipodophyllotoxins as well as anthracycline-based antibiotics such as doxorubicin have been implicated in the etiology of this form of secondary leukemia (Beaumont et al., 2003; U.S. EPA/NCEA, 1997; De Renzo et al., 1999). Leukemia secondary to treatment with topoisomerase inhibitors presents with a distinct clinical picture compared to secondary leukemia associated with high-dose therapy with alkylating agents. Leukemia secondary to topoisomerase II inhibition or radiation will often have a shorter latency (6–36 months) and will lack evidence of a preceding myelodysplasia (Beaumont et al., 2003; Bowen, 2000). Further, cytogenetic lesions associated with t-AML following exposure to topoisomerase inhibitors are often the same as reported in de novo leukemia (De Renzo et al., 1999; Pedersen-Bjergaard et al., 2002).

Because these drugs are relatively new, there is not a robust animal database as with the alkylating agents, particularly with respect to cancer bioassays. However, in studies with mice, the topoisomerase inhibitor bimolane (ICRF 159) produced a dose-related increase in lymphocytic leukemia in female mice and none in male mice. In another study, bimolane produced granulocytic leukemia in mice (U.S. EPA/NCEA, 1997). Etoposide induces DNA damage in rat bone marrow cells (Cierniak et al., 2004) as well as in mouse bone marrow (chromosomal aberrations, increase in mitotic index and micronucleus; Choudhury et al., 2004; Attia et al., 2003). In addition, etoposide has produced considerable myelotoxicity in humans following its use in various chemotherapy regimens (Bar-Sela et al., 2003). Similarly, teniposide produces micronuclei in mouse bone marrow (Jagetia and Aruna, 1999), in addition to severe myelotoxicity and aplastic bone marrow in humans following treatment for various types of cancer (Cascinu et al., 1997; Smit et al., 1992; Ochs et al., 1991). Both etoposide and teniposide are also mutagenic (Nakanomyo et al., 1986). Doxorubicin produces bone marrow toxicity in vitro (Lin et al., 2004) as well as in vivo in mice (Oredipe et al., 2003) and rats (To et al., 2003).

The totality of the data on topoisomerase inhibitors indicates that members of this class of chemotherapeutic drugs are car-

cinoagens with the bone marrow as one of the primary target organs. This is evidenced by the induction of leukemia in both animals and humans, as well as in vitro and in vivo data demonstrating bone marrow toxicity. Taken collectively, these data support clinical evidence for their leukemogenic potential.

C. Smoking

The relationship between cigarette smoking and increased risk of leukemia has generated considerable debate, but now smoking is generally considered a weak leukemogen. In 1979, the Surgeon General reported that smoking is a major cause or contributing factor in a variety of cancers, but did not list leukemia among them. However, many of the studies evaluated in that report did show an elevated risk of developing leukemia, but no dose response was discernable. Nonetheless, Austin and Cole (1986) suggested that there may be a causative link, especially with AML. This was a highly provocative suggestion for several reasons, not the least of which is that benzene is found and produced in cigarette smoke. As a result, there have been several follow-up studies, with mostly inconclusive findings. Some studies have reported increases in AML as well as other forms of leukemia, some have only seen increases in all types of leukemia combined, and many have been negative (Severson et al., 1990; Brownson, 1989; McLaughlin et al., 1989; Heath, 1990). Part of the problem is that the relative risk of developing AML from smoking is ~1.5 (as reported in most studies). Therefore, depending on the population size, a study could report this to be significantly elevated or not. However, in 1993, a meta-analysis was conducted that provided the single best evidence for a causative link between smoking and AML (or ANLL, acute nonlymphocytic leukemia, as it is sometimes referred to) (Brownson et al., 1993). As previously mentioned, the presence of benzene or benzene metabolites such as hydroquinone and phenol adds considerable biological plausibility to this hypothesis. In heavy smokers, the absolute dose of benzene, accumulated over a lifetime, is not trivial. Modeled estimates of the potential contribution of benzene to smoking-related risk of leukemia suggest that benzene could be responsible for approximately one-tenth to one-half of smoking-induced total leukemia mortality and up to three-fifths of smoking-related AML mortality (Korte et al., 2000). However, it must be emphasized that cigarette smoke is a highly complex mixture of numerous potential carcinogens, so that while one component (i.e., benzene) can be modeled with the hypothesis that benzene within cigarette smoke plays an etiological role in the development of leukemia, the leukemogenic effects could be due to other carcinogens. Parenthetically, although trace levels of formaldehyde are also found in cigarette smoke, there is insufficient evidence to implicate this exposure in smoking-related leukemia.

V. FORMALDEHYDE

In keeping with the demonstrated bone marrow/hematopoietic toxicity of benzene and several cancer chemotherapeutic drugs, multiple lines of evidence must be

considered in order to support the biological plausibility that exposure to formaldehyde could also cause the development of leukemia. Central to this issue is the ability to demonstrate (1) that inhaled or ingested formaldehyde can reach the bone marrow (i.e., target organ), (2) that formaldehyde which reaches the bone marrow can produce hematopoietic toxicity, and (3) that there is evidence in animal studies that exposure to formaldehyde is capable of inducing a leukemogenic response. An inability to fulfill these biologic plausibility requirements of leukemogenesis would demonstrate either (a) that formaldehyde acts through a unique and unknown mode of action or, more likely, (b) that formaldehyde is not leukemogenic, suggesting that the epidemiological findings were either incorrect or not due to formaldehyde (i.e., confounded).

A. Potential for Hematopoietic (i.e., Distant Site) Toxicity

Formaldehyde is a highly reactive substance that likely exerts its corrosive and cytotoxic effects due to its ability to readily combine with free, unprotonated amino groups of amino acids or DNA to yield hydroxymethyl amino acid derivatives and a proton (H^+). It is likely that formaldehyde toxicity occurs when intracellular levels saturate formaldehyde dehydrogenase and other metabolic detoxification activity, thereby overwhelming the natural protection against formaldehyde-induced toxicity. This would then permit unmetabolized formaldehyde to exert adverse effects locally. As shown in Figure 1, the primary metabolite of formaldehyde is formate. This reaction is catalyzed by cytosolic glutathione (GSH)-dependent formaldehyde dehydrogenase (FDH), for which GSH is required as a cofactor. The reaction of formaldehyde with GSH yields *S*-hydroxymethylglutathione (GSH conjugate) which in the presence of NAD^+ and FDH forms the thiol ester of formic acid via the action of *S*-formylglutathione hydrolase (SFGH). Formic

acid is not as reactive as formaldehyde itself and can either enter into the one-carbon metabolic pool for incorporation into other cellular components, be excreted as a salt in the urine, or be further metabolized to carbon dioxide (ATSDR, 1999).

This general sequence of events shown in Figure 1 is supported by a number of studies in rodents, monkeys, and humans suggesting that if exposure levels of formaldehyde are below concentrations that can be rapidly metabolized by tissue formaldehyde dehydrogenase and other detoxification enzymes, blood levels do not appreciably increase. As noted in ATSDR (1999):

"The lack of toxicity is likely related to rapid metabolism prior to the formaldehyde reaching the blood and blood-forming components (bone marrow). Some evidence suggests, however, that the rapid metabolic capabilities can be overwhelmed to some degree (Vargova et al., 1993), resulting in some minor alterations in blood parameters. In that study, affected male rats received a gavage dose level of 80 mg/kg/day formaldehyde for 4 weeks. This dosing method may have resulted in large doses of formaldehyde being absorbed over a shorter period of time than in the drinking water studies. In this situation, some unmetabolized formaldehyde may have been responsible for the alterations in erythrocyte count and hemoglobin and mean cellular hemoglobin values. (p.)

Heck et al. (1985) determined the effect of exposure to formaldehyde on the concentration in the blood in rats and humans. Following exposure of 8 male F-344 rats to 14.4 ppm of formaldehyde for 2 hours, the blood was collected immediately after exposure. Blood from eight unexposed rats served as controls. Analysis by gas chromatography/mass spectrometry (GCMS) showed formaldehyde concentrations of 2.24 ± 0.07 and $2.25 \pm 0.07 \mu\text{g/g}$ blood in exposed rats and controls, respectively. Formaldehyde concentrations in human venous blood from four males and two females were determined by analyzing blood samples collected before and after exposure to 1.9 ppm formaldehyde for 40 min. Average formaldehyde concentrations before and after exposure were 2.61 ± 0.14 and $2.77 \pm 0.28 \mu\text{g/g}$ blood, respectively. In neither rats nor humans was there a statistically significant effect of formaldehyde exposure on the average concentrations in the blood.

In a similar study, 3 rhesus monkeys were exposed to formaldehyde at 6 ppm, 6 h/day, 5 days/week for 4 weeks and the formaldehyde concentration in the blood was measured by gas chromatography mass spectrometry (GCMS). The formaldehyde concentrations immediately after the final exposure in the 3 exposed and 3 unexposed animals were 1.84 and $2.42 \mu\text{g/g}$ blood, respectively. Additionally, after a further 45 h without exposure to formaldehyde, blood concentrations did not differ significantly. These results demonstrate that subchronic inhalation exposure of nonhuman primates to formaldehyde has no significant effect on the concentration in the blood, and that the average concentration of formaldehyde in the blood of monkeys is similar to that observed in human studies (Casanova et al., 1988).

In order to further explore these issues, [^{14}C]- and [^3H] formaldehyde was studied for its ability to label macromolecules

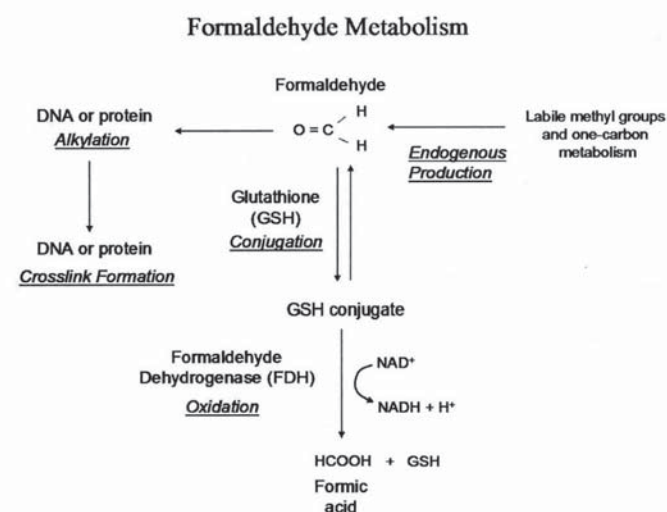


FIG. 1. Primarily metabolic pathway of formaldehyde biotransformation.

(i.e., DNA, RNA, and protein) in the respiratory and olfactory mucosa, and in the bone marrow (femur) of male Fischer 344 rats exposed for 6 h to concentrations of 0.3, 2, 6, 10, or 15 ppm, 1 day following a single preexposure to the same concentration of unlabeled formaldehyde (Casanova-Schmitz et al., 1984). The major route of nucleic acid labeling at all concentrations and in all tissues was metabolic incorporation into respiratory mucosa (i.e., metabolism of formaldehyde with subsequent entry into the one-carbon pool). Protein labeling in the respiratory mucosa was mainly due to covalent binding at the higher formaldehyde concentrations. Most important with respect to the subject of this review was the fact that while the bone marrow was heavily labeled with ^{14}C , the highest concentrations were found in DNA, suggesting that one-carbon units derived from metabolism of [^{14}C]HCHO were being used for DNA synthesis. The $^3\text{H}/^{14}\text{C}$ ratios of proteins, DNA, and RNA from bone marrow were independent of administered formaldehyde concentrations, thereby demonstrating that inhaled formaldehyde did not form covalent adducts (e.g., DNA-protein cross-linking) with macromolecules in the bone marrow.

Casanova and Heck (1987) demonstrated that depletion of glutathione (GSH) in order to inhibit the metabolism of formaldehyde did not result in inhaled formaldehyde reaching the bone marrow. In this study, rats were treated with phorone, which mainly depletes GSH, followed by exposure to [^3H]- and [^{14}C]formaldehyde at concentrations up to 10 ppm. While there were significant increases in $^3\text{H}/^{14}\text{C}$ ratios of DNA, RNA, and proteins of the nasal respiratory mucosa relative to controls, suggesting decreased metabolism and increased covalent binding in these tissues, there was no increase in the $^3\text{H}/^{14}\text{C}$ ratios of bone marrow macromolecules relative to controls. Consequently, even when formaldehyde metabolism is inhibited by GSH depletion, there was no detectable covalent binding of [^3H]- and [^{14}C]formaldehyde to bone marrow macromolecules at formaldehyde levels used in this study.

In a study designed to assess immune function and host resistance, female B6C3F1 mice were exposed via inhalation to 15 ppm HCHO for 6 h/day for 21 days (Dean et al., 1984). Immune parameters examined related to potential hematopoietic toxicity included routine hematology, bone marrow (femur) cellularity, and CFU granulocyte-macrophage (GM) analysis. Bone marrow cellularity and clonogenic potential of bone marrow derived progenitor cells were not significantly different between exposed and controls. This study provides evidence that subchronic exposure to 15 ppm formaldehyde does not damage the bone marrow and is not likely a target organ for HCHO toxicity.

In contrast, a potential adverse effect of formaldehyde on the bone marrow was reported by Kitaeva et al. (1990). In this study, female Wistar rats were exposed via inhalation to low concentrations of formaldehyde (presumably 0.4 or 1.2 ppm), 4 h/day, 5 days/week, for 4 months. There was an increased incidence of chromosomal aberrations in bone marrow cells. However, this study, as reported, is difficult to interpret since key experimen-

tal procedures (e.g., dose levels) and statistical methods were not sufficiently described. Furthermore, the overwhelming majority of studies have not corroborated this finding, including some with considerably higher exposures. Therefore, this single study is not sufficient to demonstrate formaldehyde-induced bone marrow toxicity.

There are essentially no reported hematological effects following exposure of either humans or animals to formaldehyde. While accidental ingestion of a large quantity of formaldehyde was reported to cause an intravascular coagulopathy (Burkhart et al., 1990), several reports of human ingestion of lower doses have not shown any effects on the blood or blood-forming organs (Eells et al., 1981; Freestone and Bentley, 1989; Koppel et al., 1990). In animal studies, neither inhalation exposure (Appelman et al., 1988; Kamata et al., 1997; Kerns et al., 1983; Woustersen et al., 1987) nor oral exposure (Johannsen et al., 1986; Til et al., 1988; Tobe et al., 1989) to high doses of formaldehyde has produced any evidence of adverse hematological effects. One study in rats exposed to massive oral doses of formaldehyde (e.g., 80 mg/kg for 4 weeks) reported minor alterations in erythrocyte count and hemoglobin values (Vargova et al., 1993). As noted in ATSDR (1999), the lack of hematopoietic toxicity in these studies is "likely related to rapid metabolism prior to the formaldehyde reaching the blood and blood-forming components (bone marrow)." This has been confirmed in modeling predictions based on a three-dimensional, anatomically accurate computational fluid dynamics model of rat nasal airflow and inhaled gas uptake. When integrated with a physiologically based mathematical model incorporating tissue thickness, formaldehyde diffusion, and removal by enzymatic and nonenzymatic processes, the model predicted a rapid and highly nonlinear decline in formaldehyde concentrations in nasal tissues (Georgieva et al., 2005). The inability of exogenous formaldehyde to increase blood concentrations was also confirmed by Franks (2005) in a sophisticated mathematical model for the absorption and metabolism of formaldehyde vapor by humans. The results of this model demonstrated that following inhalation exposure, the increase in formaldehyde concentration in the blood was insignificant compared to existing endogenous levels. Therefore, confirmatory of experimental studies, these models suggest that it is highly unlikely that following inhalation formaldehyde would cause toxicity at sites other than the initial site of contact.

B. In Vitro and In Vivo Genotoxicity and Cytogenetic Effects

Formaldehyde is genotoxic in numerous systems, including bacteria (e.g., *Salmonella typhimurium*, *Escherichia coli*), fungi (e.g., *Saccharomyces cerevisiae*, *Neurospora crassa*), nematodes (e.g., *Caenorhabditis elegans*), fruit flies (*Drosophila melanogaster*), mouse lymphoma cells, and human lymphocytes (Ma and Harris, 1988). As noted by ATSDR (1999), "formaldehyde has displayed genotoxic activity in the majority of studies in a variety of in vivo tests with organisms ranging from

bacteria to rodents and a variety of in vitro tests including tests with cultured human cells. The weight of evidence indicates that formaldehyde itself is capable of directly reacting with DNA, and producing genotoxic effects, especially when metabolic capacities are exceeded.” However, unanswered by any of these data is a central issue of this review, that is, do the genotoxic or cytogenetic effects of formaldehyde suggest or indicate a potential for bone marrow toxicity with subsequent progression to leukemia, particularly at doses that do not overtly overwhelm endogenous detoxification mechanisms?

For example, while an in vivo study with formaldehyde at an oral dose of 100 mg/kg reported positive effects in a mouse bone marrow micronucleus test and sister chromatid exchange (Pereira et al., 1982), lower in vivo doses (6.25 to 25 mg/kg ip) failed to produce these effects in femoral bone marrow examined for chromosomal aberrations and micronuclei (Natarajan et al., 1983). Clearly, it is possible to administer formaldehyde doses that can overwhelm or bypass detoxification mechanisms and make it to the bone marrow. However, as noted earlier, even following exposure of monkeys or rats to formaldehyde at doses of 6 and 14 ppm, respectively, blood concentrations of formaldehyde are not increased. This supports the hypothesis that at reasonably anticipated exposure levels of formaldehyde, the bone marrow would not be a site of toxicity.

There are studies that report the putative effects of formaldehyde on a variety of biomarkers, including lymphocyte DNA–protein cross-links (DPX), sister chromatid exchanges (SCE), chromosome aberrations (CA), and micronucleus assay (MN). For example, formaldehyde was reported to cause an in vitro and in vivo increase in DPX in human white blood cells taken from 12 workers exposed to formaldehyde and eight controls (Shaham et al., 1996). While there was a significant increase in DPX in white blood cells from exposed workers (anatomy department and pathology institute), the overlap with controls was notable. The increase could not be attributed to smoking, although the difference in DPC between smokers and nonsmokers appeared to be similar to the difference between exposed and nonexposed workers. The small sample limits the utility of these findings.

Shaham et al. (2002) measured SCE in peripheral lymphocytes of 90 workers from 14 hospital pathology departments who were occupationally exposed to formaldehyde and of 52 unexposed workers as controls. The SCE results were expressed as either the mean number of SCEs per chromosome or the proportion of high frequency cells (i.e., >8 SCEs), with a high correlation between these two variables. There was a significant difference between the adjusted means of both SCEs variables among the exposed group compared with that of the unexposed controls. Adjustment was made for age, sex, smoking habits, education workers, and origin. However, the significance of SCE is unknown and no prospective human study has validated this as a biomarker of human cancer risk of any type, including leukemia (Preston and Hoffman, 2001).

Suruda et al. (1993) prospectively investigated the effect of low-level exposure to formaldehyde on oral, nasal, and lymphocyte biological markers in a group of 29 mortician students who were about to take a course in embalming over an 85-day study period. Epithelial cells from the buccal area of the mouth and nose showed an increase in micronucleus frequency during the study period. In peripheral lymphocytes, the frequency of micronucleated lymphocytes significantly increased by 28%, while SCE decreased by 7.5%. There was a dose-response relationship between cumulative exposure and increases in buccal epithelial micronuclei in males, but not in females, and no dose-response relationship between changes in nasal cells and cumulative formaldehyde exposure for the entire study was reported. Additionally, there was also no correlation between cumulative formaldehyde exposure and changes in micronucleated lymphocytes. However, the significance of these findings is unknown and no prospective human study has validated micronuclei as a biomarker of human cancer risk of any type, including leukemia.

Numerous other studies have investigated the potential in vivo genotoxicity (i.e., SCE, CA, or DPX) in the peripheral lymphocytes of occupationally exposed workers compared to unexposed controls (Bauchinger and Schmid, 1985; He et al., 1998; Yager et al., 1986; Ying et al., 1997, 1999; Vasudeva and Anand, 1996; Thompson et al., 1984). As discussed later, the evidence that exposure to potentially carcinogenic chemicals is associated with an increase in SCE in peripheral lymphocytes is mixed. While these studies are of interest, the resulting data are frequently conflicting. The inability to link these markers to cancer risk of any type, particularly in a specific one target organ, is problematic for concluding that biomarkers measured in peripheral lymphocytes are indicative of an increase in leukemia risk. Also, these markers are for circulating cells, and it has not been shown that these effects occur in stem cells that can transition to leukemia.

With respect to the central issue of whether chromosomal aberrations in peripheral lymphocytes from workers with occupational exposure to formaldehyde might be an indicator of potential hematopoietic risk, Dallas et al. (1992) conducted a cytogenetic analysis of lung (i.e., pulmonary lavage fluid) and bone marrow cells in rats after repeated exposure to formaldehyde. Male Sprague-Dawley rats were exposed to 0, 0.5, 3, or 15 ppm formaldehyde for 6 h/day, 5 days/week for 1 and 8 weeks. There was an increase in pulmonary lavage cells with CA after both 1 and 8 weeks of exposure with the greatest effect in animals exposed at 15 ppm for 8 weeks. However, there were no differences in the proportion of bone marrow cells with CA between animals exposed to formaldehyde and controls at either 1 or 8 weeks at any dose level.

The target organ specificity in pulmonary cells noted by Dallas et al. (1992) was confirmed in vitro with cultured bronchial epithelial and fibroblastic cells, where formaldehyde was shown to cause single-strand DNA breaks and DNA–protein cross-links (Casanova-Schmitz et al., 1984). In contrast, the lack of effects on bone marrow cells was demonstrated in an earlier study by Dallas et al. (1987) using flow cytometry to monitor the cell-cycle distribution of DNA and RNA in bone marrow and alveolar

macrophages in male Sprague-Dawley rats exposed to formaldehyde vapor concentrations of 0, 0.5, 3, or 15 ppm for 6 h/day, 5 days/week, for up to 24 weeks. While there were clear effects on pulmonary cells following all three doses, there were no formaldehyde-related effects on bone marrow cells at any dose or time point.

The data just described demonstrate that while formaldehyde can produce dose-related cytogenetic effects on some cells following direct exposure (i.e., bronchial epithelial cells), similar effects are not observed on cells distant from the site of administration such as bone marrow. This suggests that unless formaldehyde doses that grossly exceed metabolic capabilities are administered (e.g., 100 mg/kg), distant site toxicity (including bone marrow toxicity) is unlikely.

C. Formaldehyde and Cancer

Numerous studies in rodents have been conducted to determine the carcinogenic potential of formaldehyde. With the exception of one study (i.e., Soffritti et al., 1989, 2002, reviewed in detail later), no other studies have reported a carcinogenic effect other than at the site of administration, that is, nasal cancer in rats and mice following inhalation exposure and gastric cancer in rats following ingestion exposure. As noted by Nelson et al. (1986), "No evidence of toxicity was detected at sites other than the respiratory tract. Bone marrow hyperplasia present in the rat bioassay was not considered a primary effect of formaldehyde exposure, but secondary to anoxia due to the presence of obstructive masses in the nasal passages." A detailed review by Feron et al. (1991) noted that "Following inhalation exposure at levels causing cell damage and hyperproliferative changes in the epithelium of the nasal cavity, formaldehyde has been found to cause nasal cavity tumors (mainly squamous cell carcinomas) in rats (Kerns et al., 1983; Tobe et al., 1989; Sellakumar et al., 1985; Feron et al., 1989) and probably in mice (Kerns et al., 1983) but not in hamsters (Dalbey, 1982)." Since none of these studies reported any adverse effects on the bone marrow, they are not further reviewed here. In another inhalation study by Swenberg et al. (1980), formaldehyde was administered to rats at 0, 2, 6, or 15 ppm, 6 h/day, 5 days/week, for 18 months. In total, 43 tissues were examined and, as noted by the authors, "Compound-related lesions [squamous metaplasia] were restricted to the nasal cavity."

Til et al. (1989) conducted a 2-year drinking-water study of formaldehyde in Wistar rats. The mean HCHO doses administered to male and female animals were 0, 1.2, 15, or 82 mg/kg/day and 0, 1.8, 21, or 109 mg/kg/day, respectively. Treatment-related changes were only noted in the gastric mucosa, although there was no evidence of carcinogenicity either in the stomach or any other sites.

Of the many carcinogenicity studies on formaldehyde, the only one that has reported a carcinogenic effect at a site distant from the point of administration (i.e., nasal passages or gastric mucosa) was by Soffritti et al. (1989). In this study, male and female Sprague-Dawley rats of different ages (i.e., 7 weeks old

at start, 25 weeks old at start [i.e., breeders] and 12-day embryos [i.e., in utero exposure]) were exposed to formaldehyde in drinking water at concentrations of 0, 10, 50, 100, 500, 1000, 1500, and 2500 mg/L for up to 104 weeks. Only the 7-week-old rats were exposed to graded doses of formaldehyde (i.e., 10–1500 mg/L), while the 25-week-old and in utero rats were only exposed to formaldehyde at either 0 or 2500 mg/L. In one of the "control" groups, methyl alcohol was added to the drinking water at a concentration of 15 mg/L, although there was no explanation for why this was done. Histopathology examinations were conducted on most tissues, including the femur. As reported by Soffritti et al. (1989), there was an increase in "lymphoblastic leukemias and lymphosarcomas" and "immunoblastic lymphosarcoma." While these findings were increased at doses >500 mg/L, the lack of any statistical analysis of the data precludes the ability to accurately assess the data; for example, the reported incidence of "immunoblastic lymphosarcoma" did not appear to be dose related, and "other leukemia" appeared similar in exposed and controls. There did not appear to be any differences between male and female breeder rats and controls with respect to the various leukemias reported, although again, the absence of statistical analysis makes an accurate assessment of these data impossible. Additionally, while bone marrow was one of the tissues specifically mentioned as part of routine histopathology, there was no mention of findings from this tissue. Because of the numerous questions concerning the conduct of this study, it is difficult to judge the findings in context with other data. As noted by Feron et al. (1990, 1991), none of the contradictory findings from other oral dosing studies that were available when Soffritti et al. (1989) published their results were discussed. In addition, while Soffritti et al. present their historical control data for stomach, intestine, and gastrointestinal (GI) neoplasms in Sprague-Dawley rats, historical control data for lymphoblastic leukemia-lymphosarcoma are not presented. As described by Feron et al. (1990, 1991), historical untreated control data in Sprague-Dawley rats of the colony used show that the incidence of leukemia varies widely, with reported spontaneous incidence rates similar to those reported by Soffritti et al., suggesting that treatment-related effects may have been unrelated to formaldehyde exposure. As concluded by Feron et al. (1991), "Since, however, crucial information on procedures and histopathology of non-neoplastic changes is lacking, the adequacy of this study and the relevance of the data can hardly be judged, if at all." In reviewing the results of Soffritti et al. (1989), ATSDR (1999) expressed skepticism: "Another limitation to the strength of the evidence for formaldehyde-induced leukemia is the lack of a consistent dose-response relationship in the Soffritti et al. study. . . . The second part of the Soffritti et al. (1989) study found no statistically increased incidence of leukemia in groups of breeding pairs of rats or their offspring exposed for life to the higher dose level of 313 mg/kg/day. A further limitation is the absence of corroborating evidence for effects at sites distant from portals-of-entry in the other drinking water rat studies, and in inhalation-exposure animal studies." The Cancer

Assessment Committee of the Center for Food Safety and Applied Nutrition, U.S. Food and Drug Administration (FDA), also reviewed the study of Soffritti et al. (1989), concluding that the data reported were “unreliable” due to “a lack of critical detail . . . questionable histopathological conclusions, and the use of unusual nomenclature to describe the tumors.” Consequently, the FDA “determined that there is no basis to conclude that formaldehyde is a carcinogen when ingested” (U.S. FDA, 1998). Finally, Soffritti et al. (2002) again reported the results first published as Soffritti et al. (1989). This appeared to be the same study except that the reported incidence of leukemia was almost doubled in most treatment groups, that is, 45 versus 91 in males and 34 versus 60 in females. However, information on historical control incidences of leukemia was still lacking and there was no explanation for the dramatic changes in the incidence of leukemia in the two reports.

The ability of formaldehyde to cause leukemia in animals exposed either by inhalation or ingestion must be judged in the context of all available data. Of the numerous long-term carcinogenicity studies, including exposure by inhalation or via drinking water, that have investigated the carcinogenic potential of formaldehyde, only one (i.e., Soffritti et al., 1989, 2002) has reported an increased incidence of leukemia. Leukemia was not reported in any other of seven inhalation bioassays with formaldehyde, nor was it detected in three other drinking-water studies in which rats were exposed to doses as high as 1.9 g/L or 5 g/L (Takahashi et al., 1986; Tobe et al., 1989; Til et al., 1989). As enumerated earlier, given the limitations and inconsistencies as reported by the Soffritti et al. (1989, 2002) study, it is difficult to reconcile the reported findings of leukemia with the rest of the peer-reviewed literature.

VI. CONCLUSIONS

The data on benzene and several classes of cancer chemotherapeutic drugs demonstrate a sequence of events that must occur prior to the development of leukemia in either animals or humans. First there must be evidence that a particular suspect leukemogen can reach the bone marrow following exposure. Second, there needs to be a demonstrable toxic effect on bone marrow cells that is related to leukemia pathways. Third, current models of leukemogenesis indicate that the leukemogen must be genotoxic. These key fundamental aspects of the mode of action for leukemogenic substances, such as benzene and some cancer therapeutic drugs, are simply not fulfilled by the available data on formaldehyde. With the exception of substantial exposure that is unlikely to be present in the human setting where epidemiological studies have been conducted, there is no evidence to suggest that formaldehyde reaches any target organ beyond the site of administration, such as the bone marrow. Furthermore, with the same caveat, there is no indication that formaldehyde is toxic to the bone marrow/hematopoietic system in the *in vitro* studies. Finally, any theory or hypothesis that formaldehyde might be capable of causing leukemia via a mode of action different from the above noted sequence of events (e.g., mutation of circulating

stem cells with subsequent transport to the bone marrow) should be capable of being experimentally validated. An inability to do this precludes support for this hypothesis and remains speculative. In this regard it is worthwhile to note that rats have bone marrow stem cells that move into and out of the circulation. It is therefore reasonable to expect that such stem cells could be “mutated” as blood flowed through the lungs with subsequent transport back to the bone marrow in the numerous inhalation bioassays with formaldehyde. The lack of leukemia or any evidence of bone marrow toxicity in any of these studies suggests that this hypothesized sequence of events does not occur.

The underlying biology of leukemogenesis as just outlined is also corroborated in an extensive review prepared by the National Center for Environmental Assessment of the lymphoid and hematopoietic diseases induced in humans and rodents following exposure to chemical agents known to be associated with leukemogenesis (U.S. EPA/NCEA, 1997). Included are the same chemicals used in the present review, i.e., benzene, alkylating agents and topoisomerase inhibitors. In addition to confirming the necessity of the bone marrow as a target organ for leukemogenesis, the conclusions also amplify the findings of the present review:

“By evaluating the characteristics of known leukemia-inducing agents, a number of generalizations appear to be warranted. (1) The primary type of lymphohematopoietic cancer induced by chemicals and radiation in humans is myeloid leukemia (ANLL). . . . (2) Potent human leukemia-inducing agents induce significant myelotoxicity in structural chromosomal aberrations in exposed humans. Similar effects are seen when these agents are administered to animal models. (3) Administration of human leukemia-inducing agents to mice results in increases in lymphohematopoietic tumors. However, in contrast to the human, these tumors are primarily lymphoid in origin. (4) The rat is considerably less responsive than the mouse for induction of lymphohematopoietic neoplasia following administration of human leukemogens. However, the resulting neoplasms in the rat are also are primarily lymphoid in origin.”

It should be emphasized that none of the numerous valid carcinogenicity studies in rats or mice reported any effects on lymphoid tissue as a consequence of exposure to formaldehyde.

As already described, several studies have reported associations between formaldehyde and biomarkers of exposure such as DPX, SCE, CA, and MN in peripheral lymphocytes. With the exception of CA, where only some data exists, there is insufficient evidence to conclude that an increase in these other markers predicts an increased future risk. Most investigations have studied chromosomal aberrations (CA), because it is generally accepted that chromosomal mutations are causal events in the development of cancer. However, as noted later, while some studies have reported an increased risk of total cancers, it has never been proven that increased chromosomal damage is associated with excess cancer risk of a particular disease. Two additional techniques, SCE and MN, have also been used, although the toxicological or clinical significance of these latter two methods is not fully understood (Hagmar et al., 1998a, 1998b, 2001, 2004). For example, in a pooled analysis of occupational

cohorts, 3541 subjects were examined for CA, 2703 for SCE, and 1496 for MN. While there was a significantly elevated risk of all cancer combined among subjects with high CA frequency, this was not observed for those with medium or low CA frequency. There was no association between the SCE or MN frequencies and subsequent cancer incidence/mortality. Of particular interest was the finding that the risk for high versus low levels of CA was similar in subjects heavily exposed to carcinogens and in those who had never, to their knowledge, been exposed to any carcinogenic chemicals during their lifetime. In a similar study, the risk for high versus low levels of CA was similar in subjects heavily exposed to carcinogens and in those who had never been exposed to any carcinogenic chemicals during their lifetime, once again supporting the idea that chromosome damage itself is involved in the pathway to cancer (Bonassi et al., 2000).

While chromosome damage is likely involved in the pathway to cancer, based on this kind of evidence alone, it cannot be concluded that exposure to particular chemicals is responsible for specific kinds of cancer. This view is corroborated by Preston and Hoffmann (2001), who note that "individuals with higher frequencies of chromosome aberrations for whatever reason (genetic or environmental) are as a group at greater risk of dying from cancer. This is very different from concluding that exposures to mutagens that result in a higher frequency of chromosome aberrations in peripheral lymphocytes leads to an increase risk of cancer, especially for specific tumor types." While benzene has also been reported to cause CA in peripheral lymphocytes, this is not the evidence on which the established leukemogenic potential of benzene is based. Rather, benzene was first associated with AML in humans, has documented bone marrow toxicity in humans and animals, and has also been shown to cause leukemia in rodents. Thus, although it might be hypothesized that finding CA in the peripheral lymphocytes of benzene-exposed workers is a risk factor for the subsequent development of AML, it is the antecedent knowledge that corroborates this hypothesis. There are no animal studies that report an increased rate of CA with formaldehyde exposure and the few human studies are conflicting (e.g., Thomson et al., 1984; Vasudeva and Anand, 1996; Ji-Liang et al., 1998). However, none of these data can be interpreted as indicating an increased risk of cancer, including leukemia. Thus, the limited evidence for genotoxicity in humans does not provide sufficient evidence to be corroborative of human epidemiology studies. In this regard, it is worthwhile to note that the alkylating agent methotrexate is well established as producing multiple chromosomal abnormalities in human lymphocytes both in vitro and in vivo (Mondello et al., 1984; IARC, 1987). However, after many years of observation on thousands of patients with rheumatoid arthritis, lupus, psoriasis, and various malignancies treated with methotrexate, there is no evidence of an increase risk of s-AML following prolonged use. This observation calls into question the value of citing lymphocyte chromosomal aberrations as predictive of a particular chemical's leukemogenic effect in humans.

As reviewed by Heck and Casanova (2004) as well as in this review, formaldehyde does not cause DPX or CA in bone marrow cells. This may be an important mechanistic consideration if, as described by Conolly et al. (2004), DPX as a precursor event (i.e., either descriptive or etiologic) in formaldehyde-induced nasal squamous-cell carcinoma would be similarly a precursor event in formaldehyde-induced leukemia. This would necessarily require a demonstration of formaldehyde-induced DPX in the bone marrow and not just in circulating lymphocytes as reviewed above. While it is not known if DPX is etiologically implicated in formaldehyde-induced nasal cancer, it appears to be a useful surrogate for modeling the genotoxic and cytotoxicity/regenerative cellular proliferation potential of formaldehyde (Conolly et al., 2004). The inability of formaldehyde to induce DPX in bone marrow would further support the biological implausibility of formaldehyde-induced leukemia.

The final corroboration demonstrating the biological plausibility of leukemogenesis is the ability of leukemogenic substances to actually cause the development of leukemia. Benzene and the cancer chemotherapeutic drugs considered in this review clearly fulfill this criterion by their demonstrated ability to cause leukemia in animal models. As shown by the totality of the animal carcinogenicity data on formaldehyde, there is no credible scientific evidence that exposure is capable of causing leukemia. Of the numerous inhalation or drinking-water studies on formaldehyde, all are unequivocally negative with respect to demonstrating a leukemogenic effect. Only one study (i.e., Soffritti et al., 1989, 2002) reported leukemia in rats following drinking water exposure to formaldehyde. As detailed in this review, due to the numerous deficiencies in the conduct and interpretation of this study, the results can be discounted in the context of the totality of the database.

With respect to the central theme of this review (i.e., an evaluation of the biological plausibility that formaldehyde might be leukemogenic), all of the substances considered have been associated with leukemia in humans and have also demonstrated hematopoietic toxicity and leukemia in animal models. In other words, the biological plausibility of demonstrated leukemogenesis in humans has been confirmed in animal studies and augmented by additional in vitro or in vivo data, particularly data demonstrating bone marrow toxicity. The data on benzene, the alkylating agents considered in this review (plus a few others), topoisomerase inhibitors, and radiation are summarized in Table 1.

In summary, as described in this review, as well as in the review by Heck and Casanova (2004), an extensive database demonstrates that (1) normal metabolic processes prevent formaldehyde from entering the systemic circulation, (2) the bone marrow is not a target organ for formaldehyde toxicity, (3) formaldehyde does not cause leukemia in animal studies, and (4) to the extent that formaldehyde produces cytogenetic effects in lymphocytes from exposed workers, these findings have unknown significance to the development of any particular kind

TABLE 1

Comparative data on in vivo/in vitro bone marrow/hematopoietic toxicity and leukemia induction in animals and humans of leukemogenic chemicals and formaldehyde

Substance	In vivo effects on marrow or hemato poiesis	In vitro effects on marrow or hemato poiesis	Mutagenic or genotoxic	Leukemia in animals	Leukemia in humans
Benzene	+++	+++	++	+++	+++
Cyclophosphamide ^b	+++	+++	+++	+++	+++
Myeleran ^b	+++	+++	+++	+++	+++
Chlorambucil ^b	+++	+++	+++	+++	+++
Procarbazine ^b	+++	+	+++	+++	++
Thiotepa ^b	++	+	+++	+	++
Etoposide ^c	++	++	+	+	+++
Teniposide ^c	++	++	+	+	+++
Doxorubicin ^c	++	+	+++	ND	+++
X and γ radiation	+++	++	+++	Yes	Yes
Formaldehyde	No ^a	No ^a	++	No ^a	?

Note. Adapted from IARC (1981, 1987), U.S. EPA/NCEA (1997), and other cited references. +++ = Strong unambiguous; ++ = less strong; + = weak, equivocal; ? = questionable; ND = no data; NE = nonexistent.

^aSee later discussion on formaldehyde.

^bAlkylating agent.

^cTopoisomerase inhibitor.

of cancer, including leukemia. Collectively, these data fail to corroborate the epidemiology results.

In today's regulatory climate, there is an increased emphasis on understanding the mode of action of chemical carcinogenesis as a confirmation of biological plausibility. This concept is explicitly recognized in the U.S. EPA (2005) recently finalized cancer risk assessment guidelines (e.g., "An inference of causality tends to be strengthened by consistency with data from experimental studies or other sources demonstrating plausible biological mechanisms"). Particularly with respect to the possibility that exposure to formaldehyde might be etiologically associated with leukemia, the U.S. EPA (2005) guidelines note that "It is important that the hypothesized mode of action and the events that are part of it be based on current understanding of the biology of cancer to be accepted. If the body of information under scrutiny is consistent with other examples (including structurally related agents) for which the hypothesized mode of action is accepted, the case is strengthened." The position of the International Programme on Chemical Safety (IPCS, 1999) on this issue is virtually identical. Based on the epidemiological data, it is reasonable to expect that if formaldehyde was capable of inducing leukemia in exposed workers then the abundant in vivo and in vitro data on this chemical would offer some supporting evidence of the biological plausibility of this effect consistent with the leukemogenic chemicals discussed in this review. However, based on an understanding of the biological events involved in the process of chemical leukemogenesis, it is biologically implausible that formaldehyde exposure is capable of inducing leukemia in animals or humans. This conclusion is further supported by the in-depth review by Heck and Cas-

anova (2004), who observed that "the abundance of negative evidence... is undisputed and strongly suggests that there is no delivery of inhaled formaldehyde to distant sites. Combined with the fact that formaldehyde naturally occurs throughout the body, and that multiple inhalation bioassays have not induced leukemia in animals, the negative findings provide convincing evidence that formaldehyde is not leukemogenic."

The lack of relevant mode of action data on formaldehyde when compared to the proven leukemogenic substances described in this review does not support a conclusion that it is biologically plausible that formaldehyde is capable of causing leukemia in animals, much less in humans. Consequently, there are insufficient laboratory data to conclude that there is a biologically plausible relationship between formaldehyde exposure and leukemia risk.

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REFERENCES

- Abraham, N.G. (1996). Hematopoietic effects of benzene inhalation assessed by long-term bone marrow culture. *Environ. Health Perspect.* 104 Suppl 6: 1277-1282.
- Agency for Toxic Substances and Disease Registry. (1999). *Toxicological Profile for Formaldehyde*. U.S. Department of Health and Human Services, Public Health Service, Washington, DC.

- Aksoy, M. (1989). Hematotoxicity and carcinogenicity of benzene. *Environ. Health Perspect.* **82**:193–197.
- Anderson, M., Larson, R., Mauritzson, N., Schnittger, S., Jhanwar, S., and Pedersen-Bjergaard, J. (2002). Balanced chromosome abnormalities inv(16) and t(15;17) in therapy-related myelodysplastic syndromes and acute leukemia: Report from an international workshop. *Genes Chromosomes Cancer* **33**:395–400.
- Appelman, L.M., Woutersen, R.A., and Zwart, A. (1988). One-year inhalation toxicity study of formaldehyde in male rats with a damaged or undamaged nasal mucosa. *J. Appl. Toxicol.* **8**:85–90.
- Attia, S.M., Kliesch, U., Schriever-Schwemmer, G., Badary, O.A., Hamada, F.M., and Adler, I.D. (2003). Etoposide and merbarone are clastogenic and aneugenic in the mouse bone marrow micronucleus test complemented by fluorescence in situ hybridization with the mouse minor satellite DNA probe. *Environ. Mol. Mutagen.* **41**(2):99–103.
- Austin, H., and Cole, P. (1986). Cigarette smoking and leukemia. *J. Chron. Disorders* **39**(6):417–421.
- Bar-Sela, G., Tsalic, M., Gaitini, D., Steiner, M., and Haim, N. (2003). Paclitaxel, carboplatin, and oral etoposide in advanced gastric adenocarcinoma: Association with severe myelotoxicity. *Med. Oncol.* **20**(3):291–294.
- Bauchinger, M., and Schmid, E. (1985). Cytogenetic effects in lymphocytes of formaldehyde workers of a paper factory. *Mutat. Res.* **158**:195–199.
- Beaumont, M., Sanz, M., Carli, P.M., Maloisel, X., Thomas, L., and Fenaux, P. (2003). Therapy-related acute promyelocytic leukemia. *J. Clin. Oncol.* **21**:2123–2137.
- Berger, M.R., Habs, M., and Schmähl, D. (1985). Comparative carcinogenic activity of prednimustine, chlorambucil, prednisolone and chlorambucil plus prednisolone in Sprague-Dawley rats. *Arch. Geschwulstforsch.* **55**:429–442.
- Berk, P.D., Goldberg, J.D., Silverstein, M.N., Weinfeld, A., Donovan, P.B., Ellis, J.T., Landaw, S.A., Laszlo, J., Najean, Y., Pisciotta, A.V., and Wasserman, L.R. (1981). Increased incidence of acute leukemia in polycythemia vera associated with chlorambucil therapy. *N. Engl. J. Med.* **304**:441–447.
- Bonassi, S., Hagmar, L., Stromberg, U., Montagud, A.H., Tinnerberg, H., Forni, A., Heikkilä, P., Wanders, S., Wilhardt, P., Hansteen, I.L., Knudsen, L.E., and Norppa H., (2000). Chromosomal aberrations in lymphocytes predict human cancer independently of exposure to carcinogens. European Study Group on Cytogenetic Biomarkers and Health. *Cancer Res.* **60**(6):1619–1625.
- Bowen, D.T. (2000). Oxidative stress and the myelodysplastic syndromes. *Leukocyte Res.* **24**:139–140.
- Brownson, R.C. (1989). Cigarette smoking and risk of leukemia. *J. Clin. Epidemiol.* **42**:1025–1026.
- Brownson, R.C., Novotny, T.E., and Perry, M.C. (1993). Cigarette smoking and adult leukemia: A meta-analysis. *Arch. Intern. Med.* **153**:469–475.
- Brusamolino, E., Anselmo, A., Klersy, C., et al. (1998). The risk of acute leukemia in patients treated for Hodgkin's disease is significantly higher after combined modality programs than after chemotherapy alone and is correlated with the extent of radio therapy and type and duration of chemotherapy: A case control study. *Haematologica* **83**:812–823.
- Burkhart, K.K., Kulig, K.W., and McMartin K.E. (1990). Formate levels following a formalin ingestion. *Vet. Hum. Toxicol.* **32**:135–137.
- Casanova, M., and Heck, H.d'A. (1987). Further studies of the metabolic incorporation and covalent binding of inhaled [³H]- and [¹⁴C] formaldehyde in Fischer-344 rats: Effects of glutathione depletion. *Toxicol. Appl. Pharmacol.* **89**:105–121.
- Casanova, M., Heck, H. d'A., Everitt, J. I., Harrington, W. W., Jr., and Popp, J. A. (1988). Formaldehyde concentrations in the blood of rhesus monkeys after inhalation exposure. *Food. Chem. Toxicol.* **26**:715–716.
- Casanova, M., Heck, H. d'A., and Janszen, D. (1996). Comments on "DNA-protein crosslinks, a biomarker of exposure to formaldehyde—In vitro and in vivo studies" by Shaham et al. (letter to the Editor). *Carcinogenesis* **17**:2097–2101.
- Casanova-Schmitz, M., Starr, T. B., and Heck, H. d'A. (1984). Differentiation between metabolic incorporation and covalent binding in the labeling of macromolecules in the rat nasal mucosa and bone marrow by inhaled [¹⁴C]- and [³H]formaldehyde. *Toxicol. Appl. Pharmacol.* **76**:26–44.
- Cascinu, S., Del Ferro, E., Ligi, M., Graziano, F., and Catalano, G. (1997). The clinical impact of teniposide in the treatment of elderly patients with small-cell lung cancer. *Am. J. Clin. Oncol.* **20**(5):477–478.
- Choudhury, R.C., Palo, A.K., and Sahu, P. (2004). Cytogenetic risk assessment of etoposide from mouse bone marrow. *J. Appl. Toxicol.* **24**(2):115–122.
- Chu, J., Cao, S., Ying, H., and Li, D. (1981). Experimental study of busulfan-induced leukemia in strain 615 mice [Chin.]. *Zhonghua Xueyexue Zazhi* **2**:10–13.
- Cierniak, A., Papiez, M., and Kapiszewska, M. (2004). Modulatory effect of quercetin on DNA damage, induced by etoposide in bone marrow cells and on changes in the activity of antioxidant enzymes in rats. *Rocz. Akad. Med. Białymst. Supp* **1**:167–169.
- Coggon, D., Harris, E.C., Poole, J., and Palmer, K.T. (2003). Extended follow-up of a cohort of british chemical workers exposed to formaldehyde. *JNCI* **95**(21):1608–1615.
- Cole, P., and Axten, C. (2004). Formaldehyde and leukemia: An improbable causal relationship. *Regul. Toxicol. Pharmacol.* **40**(2):107–112.
- Coltman, C.A., and Dahlberg, S. (1990). Treatment-related leukemia. *N. Engl. J. Med.* **322**:52–53.
- Conolly, R.B., Kimbell, J.S., Janszen, D., Schlosser, P.M., Kalisak, D., Preston, J., and Miller, F.J. (2004). Human respiratory tract cancer risks of inhaled formaldehyde: Dose-response predictions derived from biologically-motivated computational modeling of a combined rodent and human dataset. *Toxicol. Sci.* **82**(1):279–296.
- Cronkite, E.P. (1986). Benzene hematotoxicity and leukemogenesis. *Blood Cells* **12**:129–137.
- Cronkite, E.P., Bullis, J.E., and Inoue, T. (1984). Benzene inhalation produces leukemia in mice. *Toxicol. Appl. Pharmacol.* **75**:358–361.
- Cronkite, E.P., Drew, R.T., and Inoue, T. (1985). Benzene hematotoxicity and leukemogenesis. *Am. J. Ind. Med.* **7**:447–456.
- Cronkite, E.P., Drew, R.T., and Inoue, T. (1989). Hematotoxicity and carcinogenicity of inhaled benzene. *Environ. Health Perspect.* **82**:97–108.
- Dallas, C.E., Mellard, D.N., Theiss, J.C., Pentecost, A.R., and Fairchild, E.J. 2nd. (1987). Distribution of DNA and RNA content in the bone marrow and alveolar macrophages of rats after subchronic inhalation of formaldehyde. *Environ. Res.* **43**(1):191–202.

- Dallas, C.E., Scott, M.J., Ward, J.B., Jr, and Theiss, J.C. (1992). Cytogenetic analysis of pulmonary lavage and bone marrow cells of rats after repeated formaldehyde inhalation. *J. Appl. Toxicol.* **12**:199–203.
- Dean, J.H., Lauer, L.D., House, R.V., Murray, M.J., Stillman, W.S., Irons, R.D., Steinhagen, W.H., Phelps, M.C., and Adams, D.O. (1984). Studies of immune function and host resistance in B6C3F1 mice exposed to formaldehyde. *Toxicol. Appl. Pharmacol.* **72**(3):519–529.
- De Renzo, A., Santoro, L.F.E., Notaro, R., Pane, F., Buonaiuto, M.R., Luciano, L., and Rotoli, B. (1999). Acute promyelocytic leukemia after treatment for non-Hodgkin's lymphoma with drugs targeting topoisomerase II. *Am. J. Hematol.* **60**:300–304.
- Dunn, C.D., and Elson, L.A. (1970). The comparative effect of busulphan ("Myleran") and aminochlorambucil on haemopoietic colony forming units in the rat. *Cell Tissue Kinet.* **3**(2):131–141.
- Eells, J.T., McMartin, K.E., and Black, K. (1981). Formaldehyde poisoning: Rapid metabolism to formic acid. *J. Am. Med. Assoc.* **246**:1237–1238.
- Faiola, B., Fuller, E.S., Wong, V.A., and Recio, L. (2004). Gene expression profile in bone marrow and hematopoietic stem cells in mice exposed to inhaled benzene. *Mutat. Res.* **549**(1–2):195–212.
- Farris, G.M., Robinson, S.N., Gaido, K.W., Wong, B.A., Wong, V.A., Leonard, L., and Shah, R. (1996). Effects of low concentrations of benzene on mouse hematopoietic cells in vivo: A preliminary report. *Environ. Health Perspect.* **104**(Suppl 6):1275–1276.
- Farris, G.M., Robinson, S.N., Gaido, K.W., Wong, B.A., Wong, V.A., Hahn, W.P., and Shah, R.S. (1997). Benzene-induced hematotoxicity and bone marrow compensation in B6C3F1 mice. *Fundam. Appl. Toxicol.* **36**(2):119–129.
- Feron, V.J., Til, H.P., and Woutersen, R.A. (1990). Formaldehyde in Sprague-Dawley rats. *Toxicol. Ind. Health* **6**(6):637–639.
- Feron, V.J., Til, H.P., de Vrijer, F., Woutersen, R.A., Cassee, F.R., and van Bladeren, P.J. (1991). Aldehydes: Occurrence, carcinogenic potential, mechanism of action and risk assessment. *Mutat. Res.* **259**(3–4):363–385.
- Franks, S.J. (2005). A mathematical model for the absorption and metabolism of formaldehyde vapour by humans. *Toxicol. Appl. Pharmacol.* **206**(3):309–320.
- Freestone, J., and Bentley, A. (1989). Case of formaldehyde poisoning. *Br. J. Pharm. Pract.* **11**:20–21.
- Georgieva, A.V., Kimbell, J.S., and Schlosser, P.M. (2003). A distributed-parameter model for formaldehyde uptake and disposition in the rat nasal lining. *Inhal. Toxicol.* **15**(14):1435–1463.
- Greene, M.H., Harris, E.L., Gershenson, D.M., Malkasian, G.D., Jr, Melton, L.J., III, Dembo, A.J., Bennett, J.M., Moloney, W.C., and Boice, J.D., Jr. (1986). Melphalan may be a more potent leukemogen than cyclophosphamide. *Ann. Intern. Med.* **105**:360–367.
- Guest, I., and Uetrecht, J. (2000). Drugs toxic to the bone marrow that target the stromal cells. *Immunopharmacology* **46**(2):103–112.
- Haas, J.F., Kittelmann, B., Mehnert, W.H., Staneczek, W., Mohner, M., Kaldor, J.M., and Day, N.E. (1987). Risk of leukaemia in ovarian tumour and breast cancer patients following treatment by cyclophosphamide. *Br. J. Cancer* **55**:213–218.
- Hagmar, L., Bonassi, S., Stromberg, U., Brogger, A., Knudsen, L.E., Norppa, H., and Reuterwall, C. (1998a). Chromosomal aberrations in lymphocytes predict human cancer: A report from the European Study Group on Cytogenetic Biomarkers and Health (ESCH). *Cancer Res.* **58**(18):4117–4121.
- Hagmar, L., Bonassi, S., Stromberg, U., Mikoczy, Z., Lando, C., Hansteen, I.L., Montagud, A.H., Knudsen, L., Norppa, H., Reuterwall, C., Tinnerberg, H., Brogger, A., Forni, A., Hogstedt, B., Lambert, B., Mitelman, F., Nordenson, I., Salomaa, S., and Skerfving, S. (1998b). Cancer predictive value of cytogenetic markers used in occupational health surveillance programs: A report from an ongoing study by the European Study Group on Cytogenetic Biomarkers and Health. *Mutat. Res.* **405**(2):171–178.
- Hagmar, L., Stromberg, U., Tinnerberg, H., and Mikoczy, Z. (2001). The usefulness of cytogenetic biomarkers as intermediate endpoints in carcinogenesis. *Int. J. Hyg. Environ. Health* **204**(1):43–47.
- Hagmar, L., Stromberg, U., Bonassi, S., Hansteen, I.L., Knudsen, L.E., Lindholm, C., and Norppa, H. (2004). Impact of types of lymphocyte chromosomal aberrations on human cancer risk: Results from Nordic and Italian cohorts. *Cancer Res.* **64**(6):2258–2263.
- Hauptmann, M., Lubin, J.H., Stewart, P.A., Hayes, R.B., and Blair, A. (2003). Mortality from lymphohematopoietic malignancies among workers in formaldehyde industries. *J. Nat. Cancer Inst.* **95**(21):1615–1623.
- He, J.L., Jin, L.F., and Jin, H.Y. (1998). Detection of cytogenetic effects in peripheral lymphocytes of students exposed to formaldehyde with cytokinesis-blocked micronucleus assay. *Biomed. Environ. Sci.* **11**:87–92.
- Heath, C.W. (1990). Cigarette smoking and hematopoietic cancer. *JNCI* **82**:1800–1801.
- Heck, H., and Casanova, M. (2004). The implausibility of leukemia induction by formaldehyde: A critical review of the biological evidence on distant-site toxicity. *Reg. Toxicol. Pharmacol.* **40**(2):92–106.
- Heck, H.D., Casanova-Schmitz, M., Dodd, P.B., Schachter, E.N., Witek, T.J., and Tosun, T. (1985). Formaldehyde (CH₂O) concentrations in the blood of humans and Fischer-344 rats exposed to CH₂O under controlled conditions. *Am. Ind. Hyg. Assoc. J.* **46**:1–3.
- Hoffmann, L., Moller, P., Pedersen-Bjergaard, J., Wagne, A., Pedersen, M., and Hirsch, F.R. (1995). Therapy-related acute promyelocytic leukemia with t(15;17)(q22;q12) following chemotherapy with drugs targeting DNA topoisomerase II. A report of two cases and a review of the literature. *Ann. Oncol.* **6**:781–788.
- Hsieh, L.L., Liou, S.H., Chiu, L.L., and Chen, Y.H. (1999). Glutathione S-transferase (GST) M1 and GST T1 genotypes and hematopoietic effects of benzene exposure. *Arch. Toxicol.* **73**(2):80–82.
- Huff, J.E., Haseman, J.K., and DeMarini, D.M. (1989). Multiple-site carcinogenicity of benzene in Fischer 344 rats and B6C3F mice. *Environ. Health Perspect.* **82**:125–163.
- Infante, P.F., Rinsky, R.A., and Wagoner, J.K. (1977). Leukemia in benzene workers. *Lancet* **2**:76–78.
- International Agency for Research on Cancer (IARC). (1974). Some aromatic amines, hydrazine and related substances, N-nitroso compounds and miscellaneous alkylating agents. IARC Monogr. Eval. Carcinogenic Risks to Humans. World Health Organization.
- International Agency for Research on Cancer IARC. (1981). Some antineoplastic and immunosuppressive agents. *IARC Monogr. Eval. Carcinogen. Risks Huma.* **26**.
- International Agency for Research on Cancer. (1987). *IARC monographs on the evaluation of carcinogenic risks to humans. Overall evaluations of carcinogenicity: An updating of IARC Monographs Volumes 1 to 42. Supp. 7*. Lyon, France: World Health Organization, International Agency for Research on Cancer, pp. 38–74.

- International Agency for Research on Cancer. (2000). X-radiation and gamma (γ)-radiation. *IARC Monogr. Eval. Carcinogen. Risks Hum.* 75.
- International Agency for Research on Cancer. (2004). Formaldehyde, 2 butoxyethanol and 1-tert-butoxy-2-propanol. *IARC Monogr. Eval. Carcinogen. Risks Hum.* 82:2–9.
- International Programme for Chemical Safety. (1999). Principles for the Assessment of Risks to Human Health from Exposure to Chemicals. Environmental Health Criteria No. 210. World Health Organization.
- Irons, R.D., and Stillman, W.S. (1996a). The effects of benzene and other leukaemogenic agents on haematopoietic stem and progenitor cell differentiation. *Eur. J. Haematol. Suppl.* 60:119–124.
- Irons, R.D. and Stillman, W.S. (1996b). The process of leukemogenesis. *Environ. Health Perspect.* 104(Suppl. 6):1239–1246.
- Jagetia, G.C., and Aruna, R. (1999). Elevation of micronuclei frequency in mouse bone marrow treated with various doses of teniposide (VM-26). *Toxicol. Lett.* 104(3):203–210.
- Jandl, J.H. (1997). *Blood, Textbook of Hematology*. Little, Brown & Company, Boston.
- Johannsen, F.R., Levinas, G.J., and Tegeris, A.S. (1986). Effects of formaldehyde in the rat and dog following oral exposure. *Toxicol. Lett.* 30:1–6.
- Kamata, E., Nakadate, M., and Uchida, O. (1997). Results of a 28-month chronic inhalation toxicity study of formaldehyde in male Fischer-344 rats. *J. Toxicol. Sci.* 22:239–254.
- Kerns, W.D., Pavkov, K.L., and Donofrio, D.J. (1983b). Carcinogenicity of formaldehyde in rats and mice after long-term inhalation exposure. *Cancer Res.* 43:4382–4391.
- Kitaeva, L. V., Kitaev, E. M., and Pimenova, M. N. (1990). Cytopathic and cytogenetic effects of chronic inhalation of formaldehyde on germ and marrow cells of the female rat. *Tsitologiya* 32:1212–1216.
- Koppel, C., Baudisch, H., and Schneider, V. (1990). Suicidal ingestion of formalin with fatal complications. *Intens. Care Med.* 16:212–214.
- Korte, J.E., Hertz-Picciotto, I., Schulz, M.R., Ball, L.M., and Duell, E.J. (2000). The contribution of benzene to smoking-induced leukemia. *Environ. Health Perspect.* 108(4):333–339.
- Leone, G., Mele, L., Pulsoni, A., Equitani, F., and Pagano, L. (1999). The incidence of secondary leukemias. *Haematologica* 84:937–945.
- Lin, H., She, Y.H., Cassileth, B.R., Sirotak, F., and Cunningham Rundles, S. (2004). Maitake beta-glucan MD-fraction enhances bone marrow colony formation and reduces doxorubicin toxicity in vitro. *Int. Immunopharmacol.* 4(1):91–99.
- Linet, M.S., Yin, S.N., Travis, L.B., Li, C.Y., Zhang, Z.N., Li, D.G., Rothman, N., Li, G.L., Chow, W.H., Donaldson, J., Dosemeci, M., Wacholder, S., Blot, W.J., Hayes, R.B., Wang, Y.Z., Dai, T.R., Chao, X.J., Qing, C., Jiang, Z.L., Zhang, W.U., Ye, P.Z., Kou, Q.R., Fan, Y.H., and Zhang, X.C. (1996). Clinical features of hematopoietic malignancies and related disorders among benzene-exposed workers in China. *Environ. Health Perspect.* 104(Suppl. 6):1353–1364.
- Lohrmann, H.P., and Schreml, W. (1982). Cytotoxic drugs and the granulopoietic system. *Recent Results Cancer Res.* 81:1–222.
- Ma, T.H., and Harris, M.M. (1988). Review of the genotoxicity of formaldehyde. *Mutat. Res.* 196(1):37–59.
- Marsh, G.M., and Youk, A.O. (2004). Reevaluation of mortality risks from leukemia in the formaldehyde cohort study of the National Cancer Institute. *Regul. Toxicol. Pharmacol.* 40(2):113–124.
- McLaughlin, J.K., Hrubec, Z., Linet, M.S., Heineman, E.F., Blot, W.J., Fraumeni, J.F., Jr. 1989. Cigarette smoking and leukemia. *JNCI* 81:1262–1263.
- Medinsky, M.A., Kenyon, E.M., Seaton, M.J., and Schlosser, P.M. (1996). Mechanistic considerations in benzene physiological model development. *Environ. Health Perspect.* 104(Suppl. 6):1399–404.
- Mondello, C., Giorgi, R., and Nuzzo, F. (1984). Chromosomal effects of methotrexate on cultured human lymphocytes. *Mutat. Res.* 139(2):67–70.
- Morley, A., and Blake, J. (1974). An animal model of chronic aplastic marrow failure. I. Late marrow failure after busulfan. *Blood* 44:49–56.
- Nakanomyo, H., Hiraoka, M. and Shiraya, M. (1986). Mutagenicity tests of etoposide and teniposide. *J. Toxicol. Sci. Suppl.* 1:301–10.
- Natarajan, A.T., Darroudi, F. Bussman, C.J., and van Kesteren-van Leeuwen, A.C. (1983). Evaluation of the mutagenicity of formaldehyde in mammalian cytogenetic assays in vivo and vitro. *Mutat. Res.* 122(3–4):355–360.
- National Toxicology Program. (1994). Seventh Annual Report on Carcinogens: 1994 Summary. National Toxicology Program. Benzene. U.S. DHHS, PHS, Washington, DC.
- Nelson, N., Levine, R.J., Albert, R.E., Blair, A.E., Griesemer, R.A., Landrigan, P.J., Stayner, L.T., and Swenberg, J.A. (1986). Contribution of formaldehyde to respiratory cancer. *Environ. Health Perspect.* 70:23–35.
- Niculescu, R., and Kalf, G.F. (1995). A morphological analysis of the short-term effects of benzene on the development of the hematological cells in the bone marrow of mice and the effects of interleukin-1 alpha on the process. *Arch. Toxicol.* 69(3):141–148.
- Ochs, J., Rodman, J., Abromowitch, M., Kavanagh, R., Harris, M., Yalowich, J., and Rivera, G.K. (1991). A phase II study of combined methotrexate and teniposide infusions prior to reinduction therapy in relapsed childhood acute lymphoblastic leukemia: A Pediatric Oncology Group study. *J. Clin. Oncol.* 9(1):139–144.
- Oredipe, O.A., Furbert-Harris, P.M., Laniyan, I., Green, W.R., Griffin, W.M., and Sridhar, R. (2003). Mice primed with swainsonine are protected against doxorubicin-induced lethality. *Cell Mol. Biol.* 49(7):1089–1099.
- Park, D.J., and Koeffler, H.P. (1996). Therapy-related myelodysplastic syndromes. *Semin. Hematol.* 33:256–273.
- Parke, D.V. (1996). Personal reflections on 50 years of study of benzene toxicology. *Environ. Health Perspect.* 104(Suppl. 6):1123–1128.
- Pedersen-Bjergaard, J., Erbsbøll, J., Sørensen, H.M., Keiding, N., Larsen, S.O., Philip, P., Larsen, M.S., Schultz, H., and Nissen, N.I. (1985). Risk of acute nonlymphocytic leukemia and preleukemia in patients treated with cyclophosphamide for non-Hodgkin's lymphomas. Comparison with results obtained in patients treated for Hodgkin's disease and ovarian carcinoma with other alkylating agents. *Ann. Intern. Med.* 103:195–200.
- Pedersen-Bjergaard, J., Andersen, M. K., Christiansen, D. H., and Nerlov, C. (2002). Genetic pathways in therapy-related myelodysplasia and acute myeloid leukemia. *Blood* 99(6):1909–1912.
- Pereira, M.A., Chang, L.W., and McMillan, L. (1982). Battery of short-term tests in laboratory animals to corroborate the detection of human population exposures to genotoxic chemicals. [Abstract]. *Environ. Mutagen.* 4:317.
- Petru, E., Berger, M.R., and Schmah, D. (1989). Long-term carcinogenicity of cyclophosphamide in two mouse strains with different spontaneous leukemia incidence. *Cancer Lett.* 44(3):221–226.
- Pinkerton, L.E., Hein, M.J., and Stayner, L.T. (2004). Mortality among a cohort of garment workers exposed to formaldehyde: An update. *Occup. Environ. Med.* 61(3):193–200.

- Preston, R.J. and Hoffmann, G.R. (2001). Genetic toxicology. In: *Casarett & Doull's Toxicology: The Basic Science of Poisons*, 6th ed., Klaassen, C.D., ed. McGraw-Hill, New York.
- Pui, C.H., Ribeiro, R.C., et al. (1991). Acute myeloid leukemia in children treated with epipodophyllotoxins for acute lymphoblastic leukemia. *N. Engl. J. Med.* **325**:1682–1687.
- Reimer, R.R., Hoover, R., Fraumeni, J.F., Jr, and Young, R.C. (1977). Acute leukemia after alkylating-agent therapy of ovarian cancer. *N. Engl. J. Med.* **297**:177–181.
- Schmahl, D., and Habs, M. (1978). Experimental carcinogenesis of antitumour drugs. *Cancer Treat. Rev.* **5**(4):175–184.
- Seidel, H.J., Barthel, E., and Zinser, D. (1989). The hematopoietic stem cell compartments in mice during and after long-term inhalation of three doses of benzene. *Exp. Hematol.* **17**:300–303.
- Sevenson, R.K., Davis, S., Heuser, L., Daling, J.R., and Thomas, D.B. (1990). Cigarette smoking and acute nonlymphocytic leukemia. *Am. J. Epidemiol.* **132**:418–422.
- Shaham, J., Bomstein, Y., Meltzer, A., Kaufman, Z., Palma, E., and Ribak, J. (1996). DNA–protein crosslinks, a biomarker of exposure to formaldehyde-in vitro and in vivo studies. *Carcinogenesis* **17**:121–125.
- Shaham, J., Gurvich, R., and Kaufman, Z. (2002). Sister chromatid exchange in pathology staff occupationally exposed to formaldehyde. *Mutat. Res.* **15**:115–123.
- Smit, E.F., Splinter, T.A., and Kok, T.C. (1992). A phase I study of daily oral teniposide for 20 days. *Semin. Oncol. Suppl.* **6**:40–42.
- Snyder, C.A., Goldstein, B.D., and Sellakumar, A.R. (1984). Evidence for hematotoxicity and tumorigenesis in rats exposed to 100 ppm benzene. *Am. J. Ind. Med.* **5**:429–434.
- Snyder, R. (2000). Recent developments in the understanding of benzene toxicity and leukemogenesis. *Drug Chem. Toxicol.* **23**(1):13–25.
- Snyder, R., and Hedli, C.C. (1996). An overview of benzene metabolism. *Environ Health Perspect.* **104**(Suppl. 6):1165–1171.
- Snyder, R., and Kalf, G.F. (1994). A perspective on benzene leukemogenesis. *Crit. Rev. Toxicol.* **24**:177–209.
- Soffritti, M., Maltoni, C., Maffei, R. and Biagi, R. (1989). Formaldehyde: An experimental multipotential carcinogen. *Toxicol. Ind. Health* **5**(5):699–630.
- Soffritti, M., Belpiggi, F., Lambertini, L., Lauriola, M., Padovani, M., and Maltoni, C. (2002). Results of long-term experimental studies on the carcinogenicity of formaldehyde and acetaldehyde in rats. *Ann. NY Acad. Sci.* **982**:87–105.
- Stillman, W.S., Varella-Garcia, M., and Irons, R.D. (2000). The benzene metabolite, hydroquinone, selectively induces 5q31- and -7 in human CD34+CD19- bone marrow cells. *Exp. Hematol.* **28**(2):169–176.
- Stoner, G.D., Shimkin, M.B., Kniazeff, A.J., Weisburger, J.H., Weisburger, E.K. and Gori, G.B. (1973). Test for carcinogenicity of food additives and chemotherapeutic agents by the pulmonary tumor response in strain A mice. *Cancer Res.* **33**:3069–3085.
- Stott, H., Stephens, R.J., Fox, W., and Roy, D.C. (1976). 5-Year follow-up of cytotoxic chemotherapy as an adjuvant to surgery in carcinoma of the bronchus. *B. J. Cancer* **34**(2):167–173.
- Suruda, A., Schulte, P., Boeniger, M., Hayes, R.B., Livingston, G.K., and Steenland, K. (1993). Cytogenetic effects of formaldehyde exposure in students of mortuary science. *Cancer Epidemiol. Biomarkers Prev.* **2**:453–460.
- Swenberg, J.A., Kerns, W.D., Mitchell, R.I., Gralla, E.J., and Pavkov, K.L. (1980). Induction of squamous cell carcinomas of the rat nasal cavity by inhalation exposure to formaldehyde vapor. *Cancer Res.* **40**(9):3398–402.
- Takahashi, M., Hasegawa, R., Furukawa, F., Toyoda, K., Sato, H., and Hayashi, Y. (1986). Effects of ethanol, potassium metabisulfite, formaldehyde and hydrogen peroxide on gastric carcinogenesis in rats after initiation with *N*-methyl-*N*-nitrosoguanidine. *Jpn. J. Cancer Res.* **77**:118–124.
- Thomson, E.J., Shackleton, S., and Harrington, J.M. (1984). Chromosome aberrations and sister-chromatid exchange frequencies in pathology staff occupationally exposed to formaldehyde. *Mutat. Res.* **141**:89–93.
- Til, H.P., Woutersen, R.A., and Feron, V.J. (1988). Evaluation of the oral toxicity of acetaldehyde and formaldehyde in a 4-week drinking-water study in rats. *Food Chem. Toxicol.* **26**:447–452.
- Til, H.P., Woutersen, R.A., Feron, V.J., Hollanders, V.H., Falke, H.E., and Clary, J.J. (1989). Two-year drinking-water study of formaldehyde in rats. *Food Chem. Toxicol.* **27**(2):77–87.
- To, H., Ohdo, S., Shin, M., Uchimaru, H., Yukawa, E., Higuchi, S., Fujimura, A., and Kobayashi, E. (2003). Dosing time dependency of doxorubicin-induced cardiotoxicity and bone marrow toxicity in rats. *J. Pharm. Pharmacol.* **55**(6):803–810.
- Tobe, M., Natio, K., and Kurokawa, Y. (1989). Chronic toxicity study on formaldehyde administered orally to rats. *Toxicology* **56**:79–86.
- Trainor, K.J., and Morley, A.A. (1976). Screening of cytotoxic drugs for residual bone marrow damage. *J. Natl. Cancer Inst.* **57**(6):1237–1239.
- Trainor, K.J., Seshadri, R.S., and Morley, A.A. (1979). Residual marrow injury following cytotoxic drugs. *Leukocyte. Res.* **3**(4):205–210.
- U.S. Environmental Protection Agency. (2005). Guidelines for Carcinogen Risk Assessment. Risk Assessment Forum, U.S. EPA, Washington, Dc. EPA/630/P-03/001B.
- U.S. Environmental Protection Agency, National Center for Environmental Assessment. (1997). Chemical and Radiation Leukemogenesis in Humans and Rodents and the Value of Rodent Models for Assessing Risks of Lymphohematopoietic Cancers. ORD, U.S. EPA, EPA600R-97/090. Washington, DC.
- U.S. Food and Drug Administration. (1998). Indirect food additives, adjuvants, production aids, and sanitizers. *Fed. Reg.* **63**:35134–35135.
- Valeriote, F.A., and Tolen, S.J. (1972). Survival of hematopoietic and lymphoma colony-forming cells in vivo following the administration of a variety of alkylating agents. *Cancer Res.* **32**(3):470–476.
- Van Putten, L.M., and Lelieveld, P. (1971). Factors determining cell killing by chemotherapeutic agents in vivo. II. Melphalan, chlorambucil and nitrogen mustard. *Eur. J. Cancer* **7**(1):11–16.
- Vargova, M., Wagnerova, J., and Liskova, A. (1993). Subacute immunotoxicity study of formaldehyde in male rats. *Drug Chem. Toxicol.* **16**:255–275.
- Vasudeva, N., and Anand, C. (1996). Cytogenetic evaluation of medical students exposed to formaldehyde vapor in the gross anatomy dissection laboratory. *J. Am. Coll. Health* **44**:177–179.
- Walker and Bole. (1971). Augmented incidence of neoplasia in female New Zealand black/New Zealand white mice treated with long term cyclophosphamide. *J. Lab. Clin. Med.* **78**:978–979.
- Weisburger, E.K. (1977). Bioassay program for carcinogenic hazards of cancer chemotherapeutic agents. *Cancer* **40**(4 Suppl.):1935–1949.
- Woutersen, R.A., Appleman, L.M., and Wilmer, J.W. (1987). Subchronic (13-week) inhalation toxicity study of formaldehyde in rats. *J. Appl. Toxicol.* **7**:43–49.

- Yager, J.W., Cohn, K.L., Spear, R.C., Fisher, J.M., and Morse, L. (1986). Sister-chromatid exchanges in lymphocytes of anatomy students exposed to formaldehyde-embalming solution. *Mutat. Res.* **174**:135–139.
- Ying, C.J., Yan, W.S., Zhao, M.Y., Ye, X.L., Xie, H., and Yin, S.Y. (1997). Micronuclei in nasal mucosa, oral mucosa and lymphocytes in students exposed to formaldehyde vapor in anatomy class. *Biomed. Environ. Sci.* **10**:451–455.
- Ying, C.J., Ye, X.L., Xie, H., Yan, W.S., Zhao, M.Y., and Xia, T. (1999). Lymphocyte subsets and sister-chromatid exchanges in the students exposed to formaldehyde vapor. *Biomed. Environ. Sci.* **12**:88–94.
- Yoon, B.I., Hirabayashi, Y., Kawasaki, Y., Kodama, Y., Kaneko, T., Kim, D.Y., and Inoue, T. (2001). Mechanism of action of benzene toxicity: cell cycle suppression in hemopoietic progenitor cells (CFU-GM). *Exp. Hematol.* **29**(3):278–285.

Exhibit 30

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Original Research

Evaluating biological plausibility in supporting evidence for action through systematic reviews in public health

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ABSTRACT

Objectives: The objective of this research was to develop and test methods for accessing and evaluating information on the biological plausibility of observed associations between exposures or interventions and outcomes to generate scientific evidence for action consistent with practice in systematic reviews.

Study design: To undertake this research, we used the example of the observed associations between antimicrobial use in food animals and increased risks of human exposures to antimicrobial-resistant pathogens of zoonotic origin.

Methods: We conducted a scoping search using terms related to biological plausibility or mechanism to identify key references. As recommended by these references, we also used expert consultation with researchers and a public health informationist. We used their recommendations, which included expert consultation, to identify mechanisms relevant to biological plausibility of the association we selected to test. We used the reviews conducted by the World Health Organization (WHO) Guidelines Development Group in support of reducing antimicrobial use in food animal production to populate our model for assessing biological plausibility.

Results: We were able to develop a transparent model for biological plausibility based on the adverse outcome pathway used in toxicology and ecology. We were also able to populate this model using the WHO reviews.

Conclusions: This analysis of biological plausibility used transparent and validated methods to assess the evidence used in systematic reviews based on the observational studies accessed through searches of the scientific literature. Given the importance of this topic in systematic reviews and evidence-based decision-making, further research is needed to define and test the methodological approaches to access and properly evaluate information from the scientific literature.

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Introduction

Evidence-based methods in medicine and other health-related fields have emphasized biological plausibility as an important element in assessing the strength of evidence since the work of Bradford Hill.^{1,2} As noted in a recent review of cancer risks, information on biological plausibility is particularly important as a complement to associations observed in epidemiological studies.³ For observational studies, the quality of evidence is often judged weaker than the evidence based on randomized controlled studies. These study designs, which are necessary, given the ethical ramifications of interventions in public health, are considered to be less able to eliminate the effects of residual bias. As a consequence, evaluating biological plausibility or mechanisms may be of particular value in assessing the strength of evidence from this literature. This has been recognized by several regulatory agencies, including the US Environmental Protection Agency and the European Food Safety Agency, as well as by the WHO and CODEX.^{4,5}

However, despite the importance of the topic, there are no generally accepted methods for evaluating biological plausibility, and many reviews discussing these mechanisms include only general statements on relatively non-specific physiological events or target organs with no supporting references.

Our research question concerned the biological plausibility of observed associations between antimicrobial (AM) use in agriculture and increased risks of human exposures to drug-resistant zoonotic pathogens. There are many reviews of this topic, including two recent systematic reviews. One of these systematic reviews was undertaken by the WHO Guidelines Development Group to support its task to develop evidence-based recommendations and guidelines to reduce antimicrobial resistance related to agricultural use.⁵ An additional systematic review was published independently.⁶ The WHO systematic review used the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) methodology to assess the quality of the evidence, and following the GRADE criteria, the evidence was rated of low confidence.⁷ The other systematic review⁶ used a modified GRADE approach for evaluating evidence in which the 'sufficient component' causal model proposed by Rothman was incorporated.⁸

Assessments using GRADE can cause confusion among users of guidance based on these reviews. A statement issued by the United States Department of Agriculture (USDA) shortly after the publication of the WHO guideline referred to this 'low-quality evidence' as effectively disqualifying any WHO recommendations, despite the surrounding analyses and expert opinion.⁹ To provide additional support for this evidence, we undertook an assessment of the biological plausibility of the observed associations between antimicrobial use in food animal production and increased risks of human exposures to and infections by antimicrobial-resistant zoonotic pathogens.¹⁰

Methods

We used scoping reviews and expert consultation to identify two articles with general discussions of methods related to

biological plausibility.^{11,12} From these articles, we identified the following search terms 'methods'[Subheading] OR 'methods'[All Fields] OR 'methods'[MeSH Terms] AND ('research design'[MeSH Terms] OR ('research'[All Fields] AND 'design'[All Fields]) OR 'research design'[All Fields] OR 'test'[All Fields]) AND ('biology'[MeSH Terms] OR 'biology'[All Fields] OR 'biological'[All Fields]) AND 'plausibility'[All Fields] to access articles from the biomedical literature with more detailed methods for defining causal pathways in terms of molecular and genetic mechanisms.^{3,13,14} With further expert consultation, we further accessed articles from the toxicology and ecology literature that defined mechanisms as causal pathways in the context of adverse outcome analytic methods.^{15–17} We used the adverse outcome pathway model as it more closely represents the research question we sought to investigate, that is, a series of discrete mechanistic events not as strictly limited to one molecular pathway as in Lewis et al.³ This methodology uses schematics to represent pathways, as shown in an example in Fig. 1.

To apply this model, we used a scoping review approach, including reviews, to identify sources of information on the biological plausibility of observed associations between antimicrobial use in agriculture and increased risks of human exposure to and infection by antimicrobial-resistant pathogens from food animals. We developed and populated a similar structure for this review based on a conceptual structure that represents a sequence of mechanisms involved in the emergence and dissemination of antimicrobial resistance.^{18–21} To this model, we added the routes that connect these events in agriculture to human exposure. Consistent with the WHO practice in guideline development, we sought a global sampling of articles.

Our conceptual model is shown in the following section (Fig. 2) (see Figs. 3 and 4).

In this model, antimicrobial pressure includes the following variables: volume of antimicrobial use, concentrations of antimicrobials encountered by pathogens in animal guts, duration of antimicrobial use, and use of >1 antimicrobial at a time. Selection for resistance includes both natural selection through evolutionary mechanisms and horizontal gene transfer (HGT) of one or multiple resistance genes. Resistance dissemination includes clonal expansion of resistant organisms and gene flow among organisms through HGT involving mobile genetic elements (MGEs), conjugation, and other mechanisms. Reservoirs include the resistome (defined as microbial resources of resistance genes) and the mobilome (defined as microbial resources for enabling intercellular transfers of resistance genes) that are available within microbiomes in hosts and the external environment.²² We defined human exposure pathways to include direct and indirect animal:human contact; releases from animal confinement houses; waste disposal; and consumption of food products derived from animals.^{23,24}

Results

STEP 1 Antimicrobial pressure → selection for resistance

Fundamental to our understanding of mechanisms involved in the emergence of antimicrobial resistance is the fact that

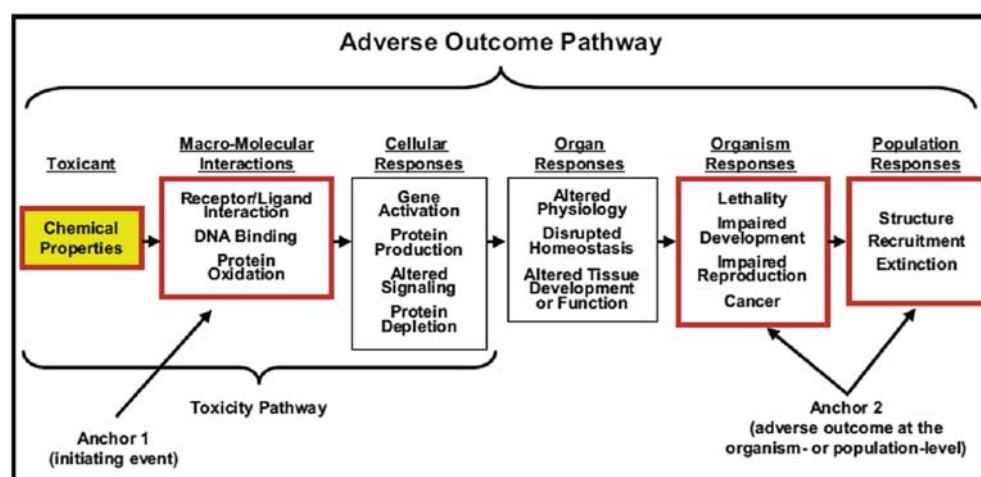


Fig. 1 – An adverse outcome pathway as used in toxicology to define events in a causal sequence connecting exposures to outcomes at the population level.¹⁵

antimicrobial resistance is inherent within microbial populations. For billions of years, microbes have produced almost all currently used antimicrobial molecules in response to intensive competition for resources and survival within the microbiome.²⁵ In this context, antimicrobial resistance (AMR) evolved as an evolutionary mechanism by which microbes survived through natural selection by random gene mutation that encoded traits that conferred resistance to these natural biotoxins.

In contrast, human uses of antimicrobials are very recent, beginning in the early 1940s. Yet due to this prehistory, resistance mechanisms were already present within bacterial populations.²⁶ During the first years of experimentation by Fleming and others, resistance was recognized as a consequence of exposure. Evolutionary theory explained the emergence of antimicrobial resistance as a process of random genetic mutations that conferred biological resistance to drugs.²⁷ This theory also supported the assumption that each instance of resistance required either vertical transmission from the replication of a resistant organism or a separate evolutionary event. At first, little was known of the specific mutations or molecular mechanisms of AMR, but with the rapid development of molecular genetics, these altered proteins were identified.²⁸

Evolutionary theory also supported the assumption that there was a cost of resistance involving a trade-off between resistance and the growth rate (the *rK* selection theory). Without this cost, bacteria would be equally likely to be resistant or susceptible in the absence of AM pressure, and with the

removal of AM pressure, the prevalence of resistant strains would decrease. However, experimental observations contradicted theory, which was amended to include more complex evolutionary responses, such as ‘bet hedging,’ by which microbial populations under AM pressure could acquire additional mutations to compensate for the cost of resistance.²⁹

Over the past 50 years, a substantial revolution has occurred in our understanding of the mechanisms by which AMR emerges and is disseminated. The current research now supports the hypothesis that HGT, rather than mutation, is the major mode by which bacteria (and other microbes) respond to antimicrobial pressure.³⁰ Horizontal or lateral gene transfer among live cells was observed, although not understood mechanistically, as early as 1928.³¹ Bacteria use several mechanisms to share resistance genes, including conjugation or exchange through direct cell:cell contact, transformation or incorporation of naked DNA from disrupted organisms in the extracellular environment, and transduction involving transfer of genetic material by transposable genetic elements.^{27,32} Later experiments demonstrated mechanisms by which donor cells initiate plasmid-mediated gene transfer and how antimicrobials stimulate intercellular signaling between susceptible and resistant bacterial strains to initiate events including gene transcription that facilitate HGT from chromosomal DNA within the donor cell and responses such as swarming within the susceptible recipient organisms.³²⁻³⁴ The mechanisms by which resistance genes that are transferred among cells can be incorporated into the chromosomal genome of the recipient cell and expressed are also understood.³⁵



Fig. 2 – A conceptual model of the mechanisms by which use of antimicrobials in food animal production increases the risks of antimicrobial resistance and exposure of human populations to pathogenic bacteria.

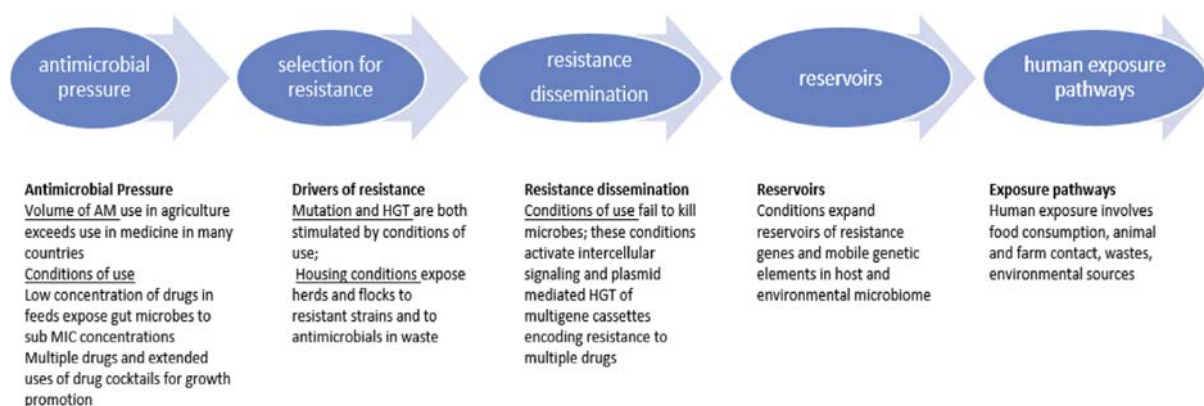


Fig. 3 – Conceptual model with an explanatory text to describe the biological plausibility between agricultural AM use and risk to human population. MIC, minimum inhibitory concentration; HGT, horizontal gene transfer; AM, antimicrobial.

Concentrations of antimicrobials

The conditions of AM use also affect resistance emergence and dissemination. The most significant overall risk factor driving AMR emergence in any setting is the volume of drug use. Associations between overall drug use and prevalence of AMR have been shown by cross-sectional comparisons of national drug use data³⁶ and longitudinally after bans on the use of certain drugs in agriculture.³⁷ In addition, the concentrations of AMs to which microbes are exposed are also significant. Exposures to subtherapeutic concentrations of AMs

(defined by bioassay at concentrations below the minimum inhibitory concentration [MIC]) are particularly effective as drivers of selection for AMR. This seemingly paradoxical observation reflects the Nietzschean aspects of bacteria that which does not kill them makes them strong. Higher concentrations of AMs (greater than or equal to the MIC) kill bacteria, whereas sublethal exposures stress but spare bacteria. As a consequence, these stressful but non-lethal conditions are particularly effective as drivers of selection for AMR through two mechanisms: increased growth and mutation rates and enhanced transfer of resistance plasmids and conjugative transposons.³⁸ The survivors acquire resistance through these mechanisms and increased incorporation of resistance genes into chromosomal DNA. Continuous or prolonged low-level AM use also expands the resistome and enhances the role of MGEs, including plasmids, in mediating the dissemination of resistance within the hosts and the environment within the microbiome.^{22,39}

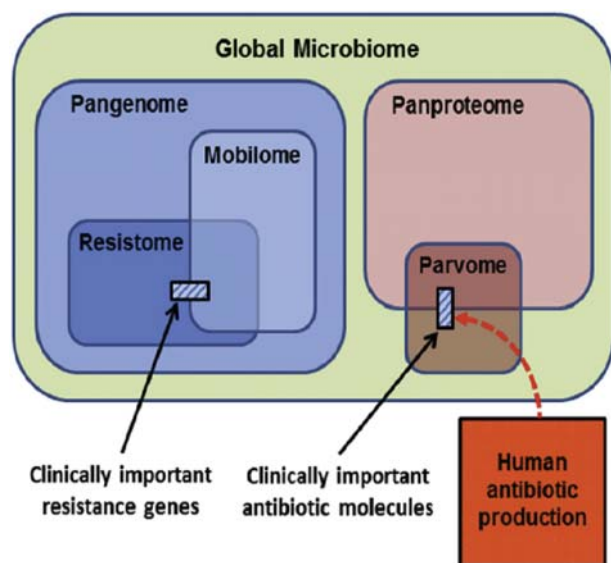


Fig. 4 – The relationships within the global microbiome and its pangenome including the resistome and the mobilome that support horizontal gene transfer in response to antimicrobial pressure including those genes encoding resistance to clinically important antimicrobials. The panproteome includes the gene products of the microbiome, including the parvome which includes clinically important antimicrobial molecules produced by humans.²²

Use of multiple drugs

Repeated exposure to multiple AMs affects the emergence and dissemination of multidrug resistance through HGT of MGEs containing multiple resistance genes encoding resistance to several drugs. This results in both cross resistance and coselection. These mechanisms were first demonstrated in 1989, with experiments showing that cross resistance among antimicrobials can be selected by one drug represented in the multidrug-resistant cassette.⁴⁰ Through HGT, bacteria not only exchange individual resistance genes but also cassettes of multiple resistance genes, which encode for coresistance to multiple antimicrobials. In other words, both pathogenic and non-pathogenic bacteria can easily share an entire cookbook of avoidance tactics rather than a single recipe. In response to repeated exposures to multiple AMs, bacteria acquire 'genetic capital' in the form of sequential acquisition of resistance genes that can be transferred as a package through transposons within the mobilome.⁴¹ These cassettes may be highly complex. *Salmonella* strain resistant to 13 antimicrobials was isolated from a child living on a farm who presented with ceftriaxone resistance; all but one of the genes encoding

multidrug resistance was on the same plasmid.⁴² These multigene cassettes can include metal resistance genes such that coselection and cross resistance can also be driven by metals such as copper, cadmium, nickel, mercury, arsenic, and zinc.^{43,44}

These conditions—use of concentrations of antimicrobials that result in subtherapeutic microbial exposures and use of multiple drugs in feeds—are common in the use of antimicrobials in poultry and livestock production. Another agricultural use is the long duration of repeated exposures for so-called prophylaxis or metaphylaxis (preventive treatment in the expectation of but absence of diagnosed disease). This may also involve sublethal concentrations of antimicrobials.⁴⁵ These low dose and extended exposures to single or multiple antimicrobials condition networks of gene flow within the microbiome such that HGT is facilitated and the role of MGEs in mediating resistance gene flow is enhanced within the gut microbiomes in animal hosts and in the environment.⁴⁶

STEP 2 Selection → Dissemination of resistance

HGT enables the rapid and efficient dissemination of resistance among bacteria (and other microbes) through highly efficient community signaling within the microbiome. This is in contrast to evolutionary mechanisms dependent on random mutation or clonal expansion. At low concentrations, horizontal transfers of resistance genes among microbes rather than vertical transmission or *de novo* mutations are now recognized as the most important mechanism and explanation for the rapid and far-ranging dissemination of resistance within and among microbial populations within hosts and the environment.⁴⁷ These mechanisms support highly efficient mobilization of community resources of resistance. As a consequence, these resources are available to microbial networks that can be geographically distant and phylogenetically distinct.

Within and among microbial communities, HGT moves individual resistance genes and cassettes of multiple genes that encode for coresistance and coselection of resistance.^{22,30} These mechanisms underlie the complexities and underscore the facility with which bacteria respond to antimicrobial pressure with both emergence and dissemination. Once a new resistance trait and gene emerges, it spreads rapidly among microbial communities. This dissemination is further facilitated by movement of bacteria through air and water, changes in methods of food animal production, and human behavior including food consumption patterns, global travel, and international trade in animals and food.

These mechanisms of dissemination are exemplified by the rapidity and global range of resistance of β -lactams as evidenced in the emergence of extended β -lactamases in response to the introduction of new cephalosporins.^{48,49} Since the isolation of the first of these drugs in 1948, there are now five generations of cephalosporins. Bacteria have rapidly responded to each generation of new cephalosporins with increasing numbers of distinct β -lactamase genes, now exceeding 1000.⁴⁸ Both resistant bacteria and resistance genes encoding extended-spectrum β -lactamase (ESBL) have spread rapidly and globally.⁵⁰ Moreover, ESBL resistance genes are frequently bundled with other resistance determinants in

transposable gene cassettes.⁵¹ Coselection has been suggested as the mechanisms for the rapidity of selection for resistance to novel cephalosporins such as carbapenem and colistin.⁵²

STEP 3 Dissemination → Reservoirs of resistance

Resistance reservoirs include the resistome (defined as the biological resources for responding to antimicrobial pressure) and the mobilome (defined as all the biological resources for transferring genes in response to pressure).²²

These reservoirs exist within microbes and as naked DNA within physiological niches such as the gut and ecological niches in the external environment. The increasing use of antimicrobials has enlarged the resistome and increased the activity of the mobilome.^{22,53} Increases in antimicrobial resistance genes and class 1 integrons have been reported in animals fed antimicrobials and have been documented in studies of soils treated with animal wastes or veterinary antimicrobials.^{47,54,55}

The environmental reservoirs of resistance may constitute the largest resources of these functions and are of specific concern in the context of agricultural uses through the release of untreated animal wastes containing resistance genes and antimicrobials that augment selection pressures within environmental microbiomes.³⁹

The environmental resistome has been a source of resistance in pathogenic bacteria isolated from humans.²⁵ Because agriculture is situated directly within the physical and biotic environment, with numerous porosities from farm to fork, gene flow within and from food animal production contributes significantly to the environmental resistome.⁵⁶ This involves both the release of antimicrobials and resistance genes. Several studies have reported concentrations of antimicrobials in sediments impacted by aquaculture which are many fold greater than the minimal inhibitory concentrations for many drugs and pathogens.⁵⁷ In addition, multiple MGEs have also been measured in soils and sediments.⁵⁴ Empirical assessments of gene flow from agriculture into environmental microbiomes in soils and sediments have been published.⁵⁸

STEP 4 Reservoirs → Exposure pathways

To evaluate the last step in this conceptual sequence, exposure of human populations to drug-resistant pathogens from food animal production, we considered the role of the mechanisms discussed previously within the conditions and context of food animal production. Many of the conditions in food animal production resemble those risk factors that are conducive to the mechanisms of AMR emergence and dissemination first identified in healthcare settings, and for which interventions and guidance programs have been developed and implemented in many countries.⁵⁹ They are exacerbated by animal stress and crowding during growth stages and transport.^{60,61}

In Fig. 2, we summarize the evidence for the role of mechanisms listed in Fig. 1 within the context of antimicrobial use in food animal production. We also indicate evidence supporting routes of exposure to these zoonotic pathogens from food animal production to human populations.

The food supply is the most significant pathway for human exposure to AMR pathogens from agriculture in terms of numbers of persons exposed, followed by multiple pathways of release to the environment. These two pathways operate both separately and in combination. In addition to consumption of food products from animals, there is an underappreciated and overlooked pathway of food-borne dissemination from the environment to crops consumed by humans. This is of particular risk when crops are grown with animal wastes (as in organic production) or with irrigation by surface water sources contaminated by run off from land disposal of animal^{62,63}.

The food and environmental pathways of exposure blur distinctions between health care and agriculture. Common sources of food are eaten inside and outside of healthcare facilities, and hospitals are located in environments where ambient air and water may be contaminated by agricultural releases. Moreover, people—patients, visitors, and healthcare personnel—move in and out of healthcare settings.⁶⁴ For this reason, there are no real barriers between the presence of

AMR in agriculture and the entrance of these same AMR pathogens into healthcare settings. These factors make it impossible to identify sources of resistance or to allocate burdens of disease between clinical and agricultural uses. This circularity is shown in Fig. 5.

Regardless of the original source of AMR, in most cases, it is not possible to separate agricultural and clinical sources of genetic determinants of resistance in pathogens isolated from human populations, because genes and pathogens originating in agriculture quickly become sources of exposures and infections in human communities and eventually move into healthcare settings, and strains in humans can be transferred to animal populations. This gene flow goes both ways. There is a well-annotated history of the cross transmission of so-called ‘livestock’ strains of MRSA (ST398) from humans to animals and from animals to humans.⁶⁵ Some studies of ESBL+genes in *Escherichia coli* isolates from animals, including carbapenemase, suggest that this may represent contamination of the agricultural environment by human wastes.⁶⁶

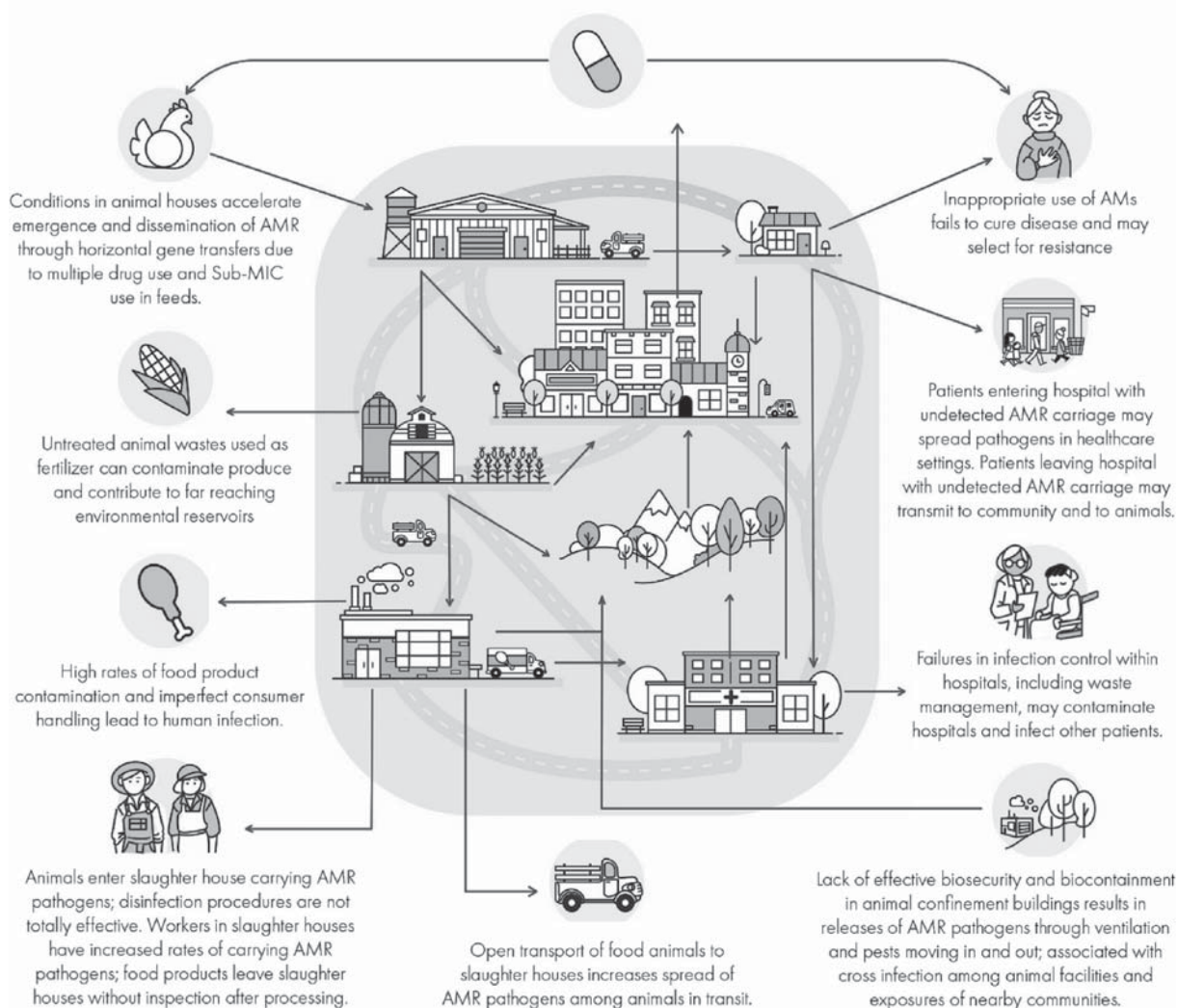


Fig. 5 – Illustration depicting complex relationships among and between multiple sources of AMR. AMR, antimicrobial resistance; MIC, minimum inhibitory concentration.

Discussion

We undertook this study to improve the evaluation of evidence related to biological plausibility of associations observed in non-RCT studies relevant to public health. The development of a transparent method for assessing the quality of these types of associations in observational studies is of high importance. The current assessment methods based on GRADE are not appropriate because of the inherent limitations of public health studies. Moreover, the use of GRADE, as in the systematic reviews conducted by the WHO, may lead to underestimation of important findings. The USDA issued a statement shortly after the publication of the WHO guideline, which referred to this 'low-quality evidence' as effectively disqualifying any WHO recommendations, despite the surrounding analyses and expert opinion.⁹ We selected the adverse outcome pathway approach based on our interest in the application of these methods for supporting the evidence derived from observational studies.

With expert consultation, we accessed articles describing general and detailed methods for organizing structural models representing biological plausibility through mechanisms that link exposures to health outcomes. One of these methods uses a comprehensive information set based on the molecular biology of cancer (Lewis et al.),³ and the other uses the more generalizable concept of adverse outcome pathways (Ankley et al.).¹⁵ We selected this latter model because of its applicability to observational studies and the substantial record of use in toxicology and ecology to support evidence-based decisions related to risk assessment.^{4,67,68} We populated our framework of adverse outcome pathway analysis, using the literature on mechanisms of antimicrobial resistance and assigned mechanistic evidence to a sequential pathway linking antimicrobial exposure of microbial communities to human exposure to drug-resistant pathogens.

We focused on mechanisms that drive microbial response to antimicrobial stress through the emergence and dissemination of resistance as well as accumulation of resistance genes and organisms in reservoirs. To this model, we added evidence on the major pathways of human exposure to AMR pathogens from agricultural sources. The conditions of agricultural use facilitate many of the mechanisms in AMR emergence and transmission, such as horizontal gene transmission and the frequency of multidrug-resistant phenotypes. By including a further focus on agricultural use, this assessment also supported the importance of the microbiome perspective. Moreover, it illustrated the role of agricultural use in expanding environmental repositories or resistomes through the direct contribution of agriculture to multiple pathways of release and from which AMR genes can be transferred to bacteria in human populations.

Conclusions

It is recognized that all uses of antimicrobials contribute to the emergence and dissemination of resistance.⁶⁹ In the context of

increasing global threats of antimicrobial resistance, we need evidence to support effective interventions to control uses of antimicrobials in both health care and agriculture. The evidence has been summarized in recent systematic reviews,^{5,6,70} which reported associations observed between agricultural use of antimicrobials for all purposes and increased risks of AMR exposure of human populations. This article adds an analysis in support of the biological plausibility of these observations, using published methods based on a mechanistic approach. We conclude that this approach may be applicable to evaluate the evidence for biological plausibility as part of an overall assessment of evidence for action-based systematic reviews on topics in which associations have been observed based on observational studies. This first application requires validation by application to other systematic reviews where the criterion of biological plausibility is of value.

Author statements

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Ethical approval and consent to participate

Not applicable.

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Competing interests

The authors declare that they have no competing interests.

Author contributions

E.K.S. and J.D. contributed equally to the conceptualization of this article and writing this manuscript. E.K.S. conducted literature searches and J.D. produced the original figures in the article. L.R. provided appropriate guidance on data collection and interpretation according to public health informationist standards and requirements. All authors read and approved the final manuscript.

Consent for publication

Not applicable.

Availability of data and material

Data sharing not applicable to this article as no data sets were generated or analyzed during the present study.

REFERENCES

- Hill AB. The environment and disease: association or causation? *Proc Roy Soc Med* 1965;58(1):295–300.
- Baral SD, Wirtz A, Sifakis F, Johns B, Walker D, Beyrer C [Internet]. *The highest attainable standard of evidence (HASTE) for HIV/AIDS interventions: toward a public health approach to defining evidence*, vol. 127. Sage Publications, Inc.; 1974. p. 572–84. Public Health Reports [cited 2018 Jan 3].
- Lewis SJ, Gardner M, Higgins JPT, Holly JMP, Gaunt TR, Perks CM, et al. Developing the WCRF International/University of Bristol methodology for identifying and carrying out systematic reviews of mechanisms of exposure-cancer associations. *Cancer Epidemiol Biomark Prev* 2017;1667–76.
- Becker RA, Dellarco V, Seed J, Kronenberg JM, Meek B, Foreman J, et al. Quantitative weight of evidence to assess confidence in potential modes of action. *Regul Toxicol Pharmacol* 2017 Jun 20;86:205–20 [Internet]. [cited 2017 May 5]. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/28232103>.
- Tang KL, Caffrey NP, Nóbrega DB, Cork SC, Ronksley PE, Barkema HW, et al. Restricting the use of antibiotics in food-producing animals and its associations with antibiotic resistance in food-producing animals and human beings: a systematic review and meta-analysis. *Lancet Planet Heal* 2017;1(8):e316–27 [Internet]. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S2542519617301419>.
- Hoelzer K, Wong N, Thomas J, Talkington K, Jungman E, Coukell A. Antimicrobial drug use in food-producing animals and associated human health risks: what, and how strong, is the evidence? *BMC Vet Res* 2017;13(1):211 [Internet]. Available from: <http://bmcvetres.biomedcentral.com/articles/10.1186/s12917-017-1131-3>.
- Norris SL, Bero L. GRADE methods for guideline development: time to evolve? *Ann Intern Med* 2016;165(11):810–1.
- Rothman KJ, Greenland S. Causation and causal inference in epidemiology. *Am J Public Health* 2005;95.
- USDA Chief Scientist Statement on WHO Guidelines on Antibiotics | USDA [Internet]. [cited 2017 Dec 16]. Available from: <https://www.usda.gov/media/press-releases/2017/11/07/usda-chief-scientist-statement-who-guidelines-antibiotics>.
- WHO. WHO guidelines on use of medically important antimicrobials in food-producing animals [Internet]. WHO; 2017 [cited 2017 Dec 16]; Available from: http://who.int/foodsafety/publications/cia_guidelines/en/.
- Khan KS, Ball E, Fox CE, Meads C. Systematic reviews to evaluate causation: an overview of methods and application. *Evid Based Med* 2012;17(5):137–41 [Internet]. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/22491154%5Cnhttp://ebm.bmj.com/content/17/5/137.full.pdf>.
- Zaza S, Wright-De Agüero LK, Briss PA, Truman BI, Hopkins DP, Hennessy MH, et al. Data collection instrument and procedure for systematic reviews in the guide to community preventive services. *Am J Prev Med* 2000;18(1 Suppl. 1):44–74.
- Ertaylan G, Le Cornet C, van Roekel EH, Jung AY, Bours MJL, Damms-Machado A, et al. A comparative study on the WCRF International/University of Bristol Methodology for systematic reviews of mechanisms underpinning exposure-cancer associations. *Cancer Epidemiol Biomarkers Prev* 2017 [Internet]. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/28754794>.
- Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, et al. Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. *Environ Health Perspect* 2016;124:713–21.
- Ankley GT, Bennett RS, Erickson RJ, Hoff DJ, Hornung MW, Johnson RD, et al. Adverse outcome pathways: a conceptual framework to support ecotoxicology research and risk assessment. *Environ Toxicol Chem* 2010;29(3):730–41.
- Galbraith D, Levy PE, Sitch S, Huntingford C, Cox P, Williams M, et al. Multiple mechanisms of Amazonian forest biomass losses in three dynamic global vegetation models under climate change. *New Phytol* 2010;187(3):647–65.
- Leist M, Ghallab A, Graepel R, Marchan R, Hassan R, Bennekou SH, et al. Adverse outcome pathways: opportunities, limitations and open questions. *Arch Toxicol* 2017;1–29.
- D'Agata EMC, Dupont-Rouzeyrol M, Magal P, Olivier D, Ruan S. The impact of different antibiotic regimens on the emergence of antimicrobial-resistant bacteria. *PLoS One* 2008;3(12):4–12.
- Alban L, Ellis-Iversen J, Andreasen M, Dahl J, Sørensen UW. Assessment of the risk to public health due to use of antimicrobials in pigs – an example of pleuromutilins in Denmark. *Front Vet Sci* 2017;4(May):74 [Internet]. Available from: <http://journal.frontiersin.org/article/10.3389/fvets.2017.00074/abstract>.
- Ashbolt NJ, Amézquita A, Backhaus T, Borriello P, Brandt KK, Collignon P, et al. Human health risk assessment (HHRA) for environmental development and transfer of antibiotic resistance. *Environ Health Perspect* 2013;121(9):993–1001.
- MacLean RC, Hall AR, Perron GG, Buckling A. The population genetics of antibiotic resistance: integrating molecular mechanisms and treatment contexts. *Nat Rev Genet* 2010;11(6):405–14 [Internet]. Available from: <https://doi.org/10.1038/nrg2778>.
- Gillings MR. Evolutionary consequences of antibiotic use for the resistome, mobilome, and microbial pangenome. *Front Microbiol* 2013;4.
- Graham JP, Nachman KE. Managing waste from confined animal feeding operations in the United States: the need for sanitary reform. *J Water Health* 2010;8(4):646–70.
- Silbergeld EK, Davis M, Leibler JH, Peterson AE. One reservoir: redefining the community origins of antimicrobial-resistant infections. *Med Clin* 2008;92(6):1391–407.

25. Perry JA, Wright GD. Forces shaping the antibiotic resistome. *BioEssays* 2014 Dec;36(12):1179–84 [Internet]. [cited 2017 May 5]. Available from: <http://doi.wiley.com/10.1002/bies.201400128>.
26. Silbergeld E. *Chickenizing farms and food*. Johns Hopkins Press; 2016.
27. Barbosa TM, Levy SB. The impact of antibiotic use on resistance development and persistence. *Drug Resist Updates* 2000;3(5):303–11 [Internet]. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S1368764600901675>.
28. Arber W. Horizontal gene transfer among bacteria and its role in biological evolution. *Life (Basel, Switzerland)* 2014 May 16;4(2):217–24 [Internet]. [cited 2017 May 5]. Available from: <http://www.mdpi.com/2075-1729/4/2/217/>.
29. Hernando-Amado S, Sanz-García F, Blanco P, Martínez JL. Fitness costs associated with the acquisition of antibiotic resistance. *Essays Biochem* 2017;61:37–48 [Internet]. (October 2016). Available from: <http://essays.biochemistry.org/content/ppebio/61/1/37.full.pdf>.
30. Von Wintersdorff CJH, Penders J, van Niekerk JM, Mills ND, Majumder S, van Alphen LB, et al. Dissemination of antimicrobial resistance in microbial ecosystems through horizontal gene transfer. *Front Microbiol* Feb 19, 2016:173 [Internet]. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26925045>.
31. Fleming A. Nobel lecture: penicillin. *Nobel lect physiol or med* 1942–1962. 1945. p. 83–93.
32. Hanahan D. Studies on transformation of *Escherichia coli* with plasmids. *J Mol Biol* 1983;166(4):557–80.
33. Yim G, Huimi Wang H, Davies FRSJ. Antibiotics as signalling molecules. *Philos Trans R Soc B Biol Sci* 2007;362(1483):1195–200 [Internet]. Available from: <http://rspb.royalsocietypublishing.org/cgi/doi/10.1098/rspb.2007.2044>.
34. Overhage J, Bains M, Brazas MD, Hancock REW. Swarming of *Pseudomonas aeruginosa* is a complex adaptation leading to increased production of virulence factors and antibiotic resistance. *J Bacteriol* 2008;190(8):2671–9.
35. Boucher Y, Labbate M, Koenig JE, Stokes HW. Integrons: mobilizable platforms that promote genetic diversity in bacteria. *Trends Microbiol* 2007;15(7):301–9.
36. Aarestrup FM, Seyfarth AM, Emborg HD, Pedersen K, Hendriksen RS, Bager F. Effect of abolishment of the use of antimicrobial agents for growth promotion on occurrence of antimicrobial resistance in fecal enterococci from food animals in Denmark. *Antimicrob Agents Chemother* 2001;45(7):2054–9.
37. Cheng AC, Turnidge J, Collignon P, Looke D, Barton M, Gottlieb T. Control of fluoroquinolone resistance through successful regulation, Australia. *Emerg Infect Dis* 2012;18(9):1453–60.
38. ter Kuile BH, Kraupner N, Brul S. In: Heipieper H, editor. *The risk of low concentrations of antibiotics in agriculture for resistance in human health care*, vol. 363; 2016 Oct. fnw210 [cited 2017 May 5]. Available from: <https://academic.oup.com/femsle/article-lookup/doi/10.1093/femsle/fnw210>.
39. Martínez JL. Antibiotics and antibiotic resistance genes in natural environments. *Science (80-)* 2008 Jul 18;321(5887):365–7 [Internet]. [cited 2017 May 5]. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18635792>.
40. Cohen SP, McMurry LM, Hooper DC, Wolfson JS, Levy SB. Cross-resistance to fluoroquinolones in multiple-antibiotic-resistant (Mar) *Escherichia coli* selected by tetracycline or chloramphenicol: decreased drug accumulation associated with membrane changes in addition to OmpF reduction. *Antimicrob Agents Chemother* 1989 Aug;vol. 33(8):1318–25 [Internet]. [cited 2017 May 18]. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/2679373>.
41. Cantón R, Morosini MI. Emergence and spread of antibiotic resistance following exposure to antibiotics. *FEMS Microbiol Rev* 2011;35(5):977–91.
42. Fey PD, Safranek TJ, Rupp ME, Dunne EF, Ribot E, Iwen PC, et al. Ceftriaxone-resistant *Salmonella* infection acquired by a child from cattle. *N Engl J Med* 2000 Apr 27;342(17):1242–9 [Internet]. [cited 2017 May 5]. Available from: <http://www.nejm.org/doi/abs/10.1056/NEJM200004273421703>.
43. Argudín MA, Lauzat B, Kraushaar B, Alba P, Agerso Y, Cavaco L, et al. Heavy metal and disinfectant resistance genes among livestock-associated methicillin-resistant *Staphylococcus aureus* isolates. *Vet Microbiol* 2016 Aug 15;191:88–95 [Internet]. [cited 2017 May 5]. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/27374912>.
44. Yu Z, Gunn L, Wall P, Fanning S. Antimicrobial resistance and its association with tolerance to heavy metals in agriculture production. *Food Microbiol* 2017;64:23–32.
45. You Y, Hilpert M, Ward MJ. Detection of a common and persistent tet(L)-carrying plasmid in chicken-waste-impacted farm soil. *Appl Environ Microbiol* 2012 May;78(9):3203–13 [Internet]. [cited 2017 May 18]. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/22389375>.
46. Cantón R, Ruiz-Garbajosa P. Co-resistance: an opportunity for the bacteria and resistance genes. *Curr Opin Pharmacol* 2011 Oct;11(5):477–85 [Internet]. [cited 2017 May 5]. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S1471489211001299>.
47. Graham DW, Knapp CW, Christensen BT, McCluskey S, Doling J. Appearance of β -lactam resistance genes in agricultural soils and clinical isolates over the 20th century. *Sci Rep* 2016 Feb 16;6(1):21550 [Internet]. [cited 2017 May 18]. Available from: <http://www.nature.com/articles/srep21550>.
48. Davies J, Davies D. Origins and evolution of antibiotic resistance. *Microbiol Mol Biol Rev* 2010;74(3):417–33 [Internet]. Available from: <http://mmbr.asm.org/cgi/content/abstract/74/3/417>.
49. Shigemura K, Tanaka K, Adachi M, Yamashita M, Arakawa S, Fujisawa M. Chronological change of antibiotic use and antibiotic resistance in *Escherichia coli* causing urinary tract infections. *J Infect Chemother* 2011;17(5):646–51 [Internet]. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21487942>.
50. Molton JS, Tambyah PA, Ang BSP, Ling ML, Fisher DA. The global spread of healthcare-associated multidrug-resistant bacteria: a perspective from Asia. Weinstein RA, editor *Clin Infect Dis* 2013 May 1;vol. 56(9):1310–8 [Internet]. [cited 2017 May 5]. Available from: <https://academic.oup.com/cid/article-lookup/doi/10.1093/cid/cit020>.
51. Skurnik D, Clermont O, Guillard T, Launay A, Danilchanka O, Pons S, et al. Emergence of antimicrobial-resistant *Escherichia coli* of animal origin spreading in humans. *Mol Biol Evol* 2016 Apr;33(4):898–914 [Internet]. [cited 2017 May 5]. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26613786>.
52. Mollenkopf DF, Stull JW, Mathys DA, Bowman AS, Feicht SM, Grooters JV, et al. Carbapenemase-Producing enterobacteriaceae recovered from the environment of a swine farrow-to-finish operation in the United States. *Antimicrob Agents Chemother* 2017 Feb 5;61(2) [Internet]. [cited 2017 May 5]. AAC.01298-16. Available from: <http://aac.asm.org/lookup/doi/10.1128/AAC.01298-16>.
53. Ravi A, Avershina E, Foley SL, Ludvigsen J, Storrø O, Øien T, et al. *The commensal infant gut meta-mobilome as a potential reservoir for persistent multidrug resistance integrons*, vol. 5; 2015 Oct 28. p. 15317 [cited 2017 May 5]. Available from: <http://www.nature.com/articles/srep15317>.
54. Muirinen J, Stedtfeld R, Karkman A, Pärnänen K, Tiedje J, Virta M. Influence of manure application on the environmental resistome under Finnish agricultural practice

- with restricted antibiotic use. *Environ Sci Technol* 2017;51(11):5989–99.
55. Cleary DW, Bishop AH, Zhang L, Topp E, Wellington EMH, Gaze WH. Long-term antibiotic exposure in soil is associated with changes in microbial community structure and prevalence of class 1 integrons. *FEMS Microbiol Ecol* 2016;92(10).
 56. Davis MF, Price LB, Liu CM-HH, Silbergeld EK. An ecological perspective on U.S. industrial poultry production: the role of anthropogenic ecosystems on the emergence of drug-resistant bacteria from agricultural environments. *Current Opinion Microbiol* Jun, 2011:244–50 [Internet]. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21621451>.
 57. Cabello FC, Godfrey HP, Tomova A, Ivanova L, Dölz H, Millanao A, et al. Antimicrobial use in aquaculture re-examined: its relevance to antimicrobial resistance and to animal and human health. *Environ Microbiol* 2013;15(7):1917–42.
 58. Zhu YG, Zhao Y, Li B, Huang CL, Zhang SY, Yu S, et al. Continental-scale pollution of estuaries with antibiotic resistance genes. *Nat Microbiol* 2017;2.
 59. You Y, Silbergeld EK. Learning from agriculture: understanding low-dose antimicrobials as drivers of resistome expansion. *Front Microbiol* 2014;5.
 60. Hayes JR, English LL, Carr LE, Wagner DD, Joseph SW. Multiple-antibiotic resistance of *Enterococcus* spp. isolated from commercial poultry production environments. *Applied Environ Microbiol* 2004;70(10):6005–11.
 61. Berriman ADC, Clancy D, Clough HE, Armstrong D, Christley RM. Effectiveness of simulated interventions in reducing the estimated prevalence of *Salmonella* in UK pig herds. *PLoS One* 2013;8(6).
 62. van Hoek AHAM, Veenman C, van Overbeek WM, Lynch G, de Roda Husman AM, Blaak H. Prevalence and characterization of ESBL- and AmpC-producing Enterobacteriaceae on retail vegetables. *Int J Food Microbiol* 2015;204:1–8 [Internet]. [cited 2017 May 18]. Available from: <http://www.sciencedirect.com/science/article/pii/S0168160515001531>.
 63. Ben Said L, Jouini A, Klibi N, Dziri R, Alonso CA, Boudabous A, et al. Detection of extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae in vegetables, soil and water of the farm environment in Tunisia. *Int J Food Microbiol* 2015 Jun 16;203:86–92 [Internet]. [cited 2017 May 18]. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S0168160515001129>.
 64. Leibler JH, Dalton K, Pekosz A, Gray GC, Silbergeld EK. Epizootics in industrial livestock production: preventable gaps in biosecurity and biocontainment. *Zoonoses Public Heal* 2017;64:137–45.
 65. Price LB, Stegger M, Hasman H, Aziz M, Larsen J, Andersen PS, et al. *Staphylococcus aureus* CC398: host adaptation and emergence of methicillin resistance in livestock. *MBio* 2012;3(1):1–6.
 66. Agersø Y, Wulff G, Vaclavik E, Halling-Sørensen B, Jensen LB. Effect of tetracycline residues in pig manure slurry on tetracycline-resistant bacteria and resistance gene tet(M) in soil microcosms. *Environ Int* 2006;32(7):876–82.
 67. Villeneuve DL, Crump D, Garcia-Reyero N, Hecker M, Hutchinson TH, LaLone CA, et al. Adverse outcome pathway (AOP) development I: strategies and principles. *Toxicol Sci* 2014;142(2):312–20.
 68. Patlewicz G, Simon TW, Rowlands JC, Budinsky RA, Becker RA. Proposing a scientific confidence framework to help support the application of adverse outcome pathways for regulatory purposes. *Regul Toxicol Pharmacol* 2015;71(3):463–77 [Internet]. Available from: <https://doi.org/10.1016/j.yrtph.2015.02.011>.
 69. O'Brien TF. The global epidemic nature of antimicrobial resistance and the need to monitor and manage it locally. *Clin Infect Dis* 1997 Jan;24(Suppl. 1):S2–8 [Internet]. [cited 2017 May 18]. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/8994775>.
 70. Hoelzer K, Wong N, Thomas J, Talkington K, Jungman E, Coukell A. Antimicrobial drug use in food-producing animals and associated human health risks: what, and how strong, is the evidence? *BMC Vet Res* 2017;13(1):211 [Internet]. Available from: <http://bmcvetres.biomedcentral.com/articles/10.1186/s12917-017-1131-3>.

Exhibit 31

1 IN THE UNITED STATES DISTRICT COURT
2 FOR THE EASTERN DISTRICT OF NEW JERSEY

3 -----)
4 IN RE JOHNSON & JOHNSON)
5 TALCUM POWDER PRODUCTS)
6 MARKETING, SALES) MDL NO.
7 PRACTICES, AND PRODUCTS) 16-2738 (FLW) (LHG)
8 LIABILITY LITIGATION)

9 -----)
10))
11 THIS DOCUMENT RELATES TO)
12 ALL CASES)
13))

14 — — —
15 Saturday, January 19, 2019
16 — — —

17 Videotaped Deposition of ARCH I. "CHIP"
18 CARSON, M.D., Ph.D., held at the Marriott
19 Houston Medical Center, 6580 Fannin Street,
20 Houston, Texas, commencing at 9:02 a.m., on
21 the above date, before Michael E. Miller,
22 Fellow of the Academy of Professional
23 Reporters, Certified Court Reporter,
24 Registered Diplomat Reporter, Certified
25 Realtime Reporter and Notary Public.

26 — — —
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VIDEOGRAPHER:
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Golkow Litigation Services

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DEPOSITION EXHIBITS	
ARCH I. "CHIP" CARSON, M.D., Ph.D.	
January 19, 2019	
NUMBER	PAGE
Exhibit 1	Notice of Deposition
Exhibit 2	11/16/18 Carson Expert Report
Exhibit 3	Carson Curriculum Vitae
Exhibit 4	Listing of Literature Reviewed
Exhibit 5	2019 Longo et al Publication
Exhibit 6	2019 Fletcher et al Publication
Exhibit 7	Undated Taher et al Publication
Exhibit 8	1952 Graham et al Publication
Exhibit 9	12/18 Health Canada Draft Screening Assessment
Exhibit 10	1/1/14 FDA Letter to Epstein
Exhibit 11	1991 Blount et al Publication
Exhibit 12	1974 Parmley et al Publication
Exhibit 13	USB Drive Containing Materials Reviewed
Exhibit 14	8/1/00 Health Canada Decision-Making Framework

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DEPOSITION EXHIBITS			PROCEEDINGS		
1	Exhibit 15	Handwritten List of	124	(January 19, 2019 at 9:02 a.m.)	
2		Materials Reviewed by		THE VIDEOGRAPHER: We are now	
3		Dr. Carson		on the record. My name is Doug	
4	Exhibit 16	1979 Chappell et al	130	Overstreet. I'm the videographer for	
5		Publication		Golkow Litigation Services. Today is	
6	Exhibit 17	2011 Reid et al Publication	159	January 19th, 2019. The time is	
7	Exhibit 18	2011 Camargo et al	163	9:02 a.m.	
8		Publication		This video deposition is being	
9	Exhibit 19	2013 Terry et al	192	held in Houston, Texas in the matter	
10		Publication		of Talcum Powder Litigation MDL	
11	Exhibit 20	2016 Cramer et al	195	No. 2738.	
12		Publication		The deponent is Dr. Chip	
13	Exhibit 21	IARC Classification Groups	225	Carson.	
14		Document		Will counsel please identify	
15	Exhibit 22	2017 Berge et al	243	themselves for the record.	
16		Publication		MS. O'DELL: Leigh O'Dell,	
17	Exhibit 23	2007 Langseth et al	247	Beasley Allen, for the plaintiffs.	
18		Publication		DR. THOMPSON: Margaret	
19	Exhibit 24	2016 Schildkraut et al	271	Thompson, Beasley Allen, for the	
20		Publication		plaintiffs.	
21	Exhibit 25	Excerpt from IARC	289	MS. KLEVORN: Amanda Klevorn,	
22		Monograph 93		Burns Charest, for the plaintiffs.	
23				MR. ZELLERS: Michael Zellers	
24					

Page 7			Page 9		
REFERENCED EXHIBITS			for the Johnson & Johnson defendants.		
1			MS. McBETH: Katherine McBeth,		
2	NUMBER	PAGE	Drinker Biddle & Reath, for the		
3	Exhibit	148	Johnson & Johnson defendants as well.		
4	Hopkins-28		MS. BOCKUS: Jane Bockus for		
5	Exhibit	148	Imerys.		
6	Pier-47		MR. DONATH: Jonathan Donath		
7	Exhibit	28	from Coughlin Duffy for Imerys.		
8	P-346		MS. APPEL: Renée Appel from		
9	--o0o--		Seyfarth Shaw for Personal Care		
10			Products.		
11			MS. TINSLEY: Caroline Tinsley,		
12			Tucker Ellis, for PTI Union, LLC and		
13			PTI Royston, LLC.		
14			THE VIDEOGRAPHER: The court		
15			reporter today is Mr. Mike Miller, and		
16			he will now swear in the witness.		
17			ARCH I. "CHIP" CARSON, M.D., Ph.D.,		
18			having been duly sworn,		
19			testified as follows:		
20			EXAMINATION		
21			BY MR. ZELLERS:		
22			Q. Can you state your name,		
23			please.		
24					

<p style="text-align: right;">Page 10</p> <p>1 A. Arch Carson.</p> <p>2 Q. You are a physician; is that</p> <p>3 right?</p> <p>4 A. I am.</p> <p>5 Q. A medical toxicologist?</p> <p>6 A. Yes.</p> <p>7 Q. We are here today to take your</p> <p>8 deposition in the talc MDL litigation</p> <p>9 proceedings; is that right?</p> <p>10 A. As far as I know, yes.</p> <p>11 Q. You are an expert witness for</p> <p>12 the plaintiffs in that litigation; is that</p> <p>13 right?</p> <p>14 A. Yes.</p> <p>15 Q. Did you receive a notice of</p> <p>16 deposition, which we'll mark as Exhibit 1, to</p> <p>17 appear here today?</p> <p>18 (Carson Deposition Exhibit 1</p> <p>19 marked.)</p> <p>20 A. Yes, I received a copy of this</p> <p>21 document.</p> <p>22 MS. O'DELL: And, Michael, just</p> <p>23 for the record, we just reassert all</p> <p>24 our previously served objections to</p>	<p style="text-align: right;">Page 12</p> <p>1 BY MR. ZELLERS:</p> <p>2 Q. As best we can, let me finish</p> <p>3 my question before you start to give your</p> <p>4 answer. I'll do the same and allow you to</p> <p>5 finish your answer before I ask you another</p> <p>6 question so our court reporter can take down</p> <p>7 what each of us say.</p> <p>8 Can you do that?</p> <p>9 A. Yes.</p> <p>10 Q. In response to the notice of</p> <p>11 deposition, which we've marked as Exhibit 1,</p> <p>12 have you brought with you certain documents</p> <p>13 here today?</p> <p>14 A. I have a collection of</p> <p>15 documents that in part respond to these</p> <p>16 requests, yes.</p> <p>17 Q. Do you have any documents in</p> <p>18 your possession that are responsive to the</p> <p>19 notice of deposition, Exhibit 1, that you</p> <p>20 have not brought here today?</p> <p>21 A. I would have to go through</p> <p>22 these things one by one, but --</p> <p>23 Q. You didn't do that before we</p> <p>24 came here today?</p>
<p style="text-align: right;">Page 11</p> <p>1 the notice.</p> <p>2 MR. ZELLERS: Thank you.</p> <p>3 BY MR. ZELLERS:</p> <p>4 Q. You have given deposition</p> <p>5 testimony in the past; is that right?</p> <p>6 A. I have.</p> <p>7 Q. On how many occasions?</p> <p>8 A. Probably 30, 35.</p> <p>9 Q. You are familiar with the</p> <p>10 procedures we're going to follow today?</p> <p>11 A. More or less, I think.</p> <p>12 Q. If at any time I ask you a</p> <p>13 question and you don't understand it, tell me</p> <p>14 you don't understand it and I'll repeat it or</p> <p>15 rephrase it to try to make it clear to you.</p> <p>16 Can you do that?</p> <p>17 A. Yes.</p> <p>18 Q. If you answer a question that I</p> <p>19 ask or that any of the counsel ask, we're</p> <p>20 going to assume that you understood it; is</p> <p>21 that fair?</p> <p>22 MS. O'DELL: Object to form.</p> <p>23 A. That's fair.</p> <p>24 ///</p>	<p style="text-align: right;">Page 13</p> <p>1 A. I did, but the plaintiffs'</p> <p>2 attorneys --</p> <p>3 MS. O'DELL: Let me just stop</p> <p>4 you, Dr. Carson, just because</p> <p>5 discussing what we've discussed is not</p> <p>6 within the purview of this deposition.</p> <p>7 That's privileged. Let me just say --</p> <p>8 THE WITNESS: All right.</p> <p>9 MS. O'DELL: -- Dr. Carson, in</p> <p>10 response to the notice, has brought</p> <p>11 with him copies of the cited materials</p> <p>12 in his report, and that's in the</p> <p>13 binder that is to his left.</p> <p>14 He's brought with him copies of</p> <p>15 certain documents that were listed on</p> <p>16 his materials considered list. He</p> <p>17 doesn't have a physical copy of</p> <p>18 everything on his materials considered</p> <p>19 list.</p> <p>20 I brought today a thumb drive</p> <p>21 that has a copy of all the items on</p> <p>22 his materials considered list. If you</p> <p>23 would like access to that, it's</p> <p>24 available to you.</p>

Page 14

1 And then in addition, he has
2 brought some additional materials that
3 he has reviewed since the service of
4 his report.

5 The only other item, as I
6 recall, on the notice of deposition
7 request for documents that has not
8 been brought to the deposition is
9 copies of invoices and Dr. Carson has
10 not sent us an invoice. That's why we
11 don't have a copy.

12 So to try to short-circuit
13 this, just to make sure since we made
14 decisions about what's produced and
15 what's not, I'll just say all that for
16 the record. And if you'd like that,
17 you're welcome to it.

18 BY MR. ZELLERS:

19 Q. Dr. Carson, you heard
20 Ms. O'Dell describe what you brought here
21 today. Is all of that accurate?

22 A. It is.

23 Q. Are you aware of there being
24 any documents or materials that are

Page 15

1 responsive to the deposition notice that you
2 have not brought with you here today?

3 A. No.

4 Q. I'm trying to understand what
5 counsel for plaintiffs, Ms. O'Dell, has said,
6 so let me ask you some questions.

7 You have brought with you today
8 in a binder some of the cited materials in
9 your report; is that right?

10 A. Yes. This is intended to be a
11 complete set of the cited references, with
12 one exception.

13 Q. When you say cited
14 references --

15 A. From my report.

16 Q. Your expert report, we will
17 mark as Exhibit 2.

18 (Carson Deposition Exhibit 2
19 marked.)

20 BY MR. ZELLERS:

21 Q. Is Deposition Exhibit 2 your
22 report in this matter?

23 A. It is. It also has
24 attachments.

Page 16

1 Q. I'll ask you about the
2 attachments in a moment.

3 Does this report,
4 Deposition Exhibit 2, contain all of the
5 opinions that you intend to offer at any
6 trial or hearing of this matter?

7 A. In general, it contains all of
8 my opinions. I expect to expand on those
9 opinions possibly in this deposition or in
10 the future.

11 Q. Today's my opportunity to ask
12 you what your opinions are in this matter.

13 As of today, are the opinions
14 that you expressed to us set forth at any
15 trial or hearing in this matter, are they
16 contained in your report, Exhibit 2?

17 A. I have seen information that
18 has become available recently that I did not
19 have at that time this report was finalized,
20 and I have modified my opinions very slightly
21 as a result of that information.

22 Q. How have you modified your
23 opinions?

24 A. My opinions have essentially

Page 17

1 been strengthened as they relate to the
2 causation question between perineal talcum
3 powder use and the occurrence of ovarian
4 cancers.

5 Q. Other than you believing that
6 your opinions are strengthened with respect
7 to the association between perineal talcum
8 powder use and ovarian cancer, have your
9 opinions changed at all since you prepared
10 your report, Exhibit 2?

11 A. No.

12 Q. Are there any new or additional
13 opinions as of today that you expect to
14 testify to at trial or any hearing of this
15 matter other than your report, Exhibit 2, and
16 as you have qualified that report by stating
17 that your opinions on association are
18 stronger today?

19 A. No.

20 MS. O'DELL: Object to the
21 form.

22 BY MR. ZELLERS:

23 Q. Okay. Your report has a list
24 of references that begin on page 11.

<p style="text-align: right;">Page 18</p> <p>1 Do you see that?</p> <p>2 A. Yes.</p> <p>3 Q. What are the references? What</p> <p>4 do they relate to? And by that, I mean --</p> <p>5 I'm just trying to understand what this list</p> <p>6 is.</p> <p>7 A. This is a list of references</p> <p>8 from which I gleaned information that were</p> <p>9 important to my forming opinions regarding</p> <p>10 the question that was given to me, and they</p> <p>11 contribute to pieces of the report in various</p> <p>12 ways.</p> <p>13 They don't represent a complete</p> <p>14 review that I made in preparing my report,</p> <p>15 but all are important in some way in terms of</p> <p>16 coming to my conclusions.</p> <p>17 Q. Are the references that you</p> <p>18 list in your report from page 11 up and</p> <p>19 through page 16, are those the materials that</p> <p>20 you are relying on in terms of your opinions</p> <p>21 that you're expressing in your report?</p> <p>22 MS. O'DELL: Objection to form.</p> <p>23 A. Yes.</p> <p>24 ///</p>	<p style="text-align: right;">Page 20</p> <p>1 I produced a report that I</p> <p>2 thought was responsive to the question that</p> <p>3 was given to me by the plaintiffs' attorneys,</p> <p>4 and within that report I felt it necessary to</p> <p>5 cite specific key references that contributed</p> <p>6 to items in that report.</p> <p>7 BY MR. ZELLERS:</p> <p>8 Q. And those are --</p> <p>9 MS. O'DELL: Excuse me, sir.</p> <p>10 Are you finished, Dr. Carson?</p> <p>11 THE WITNESS: Yes.</p> <p>12 MS. O'DELL: Okay. Sorry.</p> <p>13 BY MR. ZELLERS:</p> <p>14 Q. Those are the items that you've</p> <p>15 listed under References; is that right?</p> <p>16 A. Yes.</p> <p>17 Q. Literature are other materials</p> <p>18 that you have reviewed but didn't rise to the</p> <p>19 level of you citing them as a reference for</p> <p>20 your report, correct?</p> <p>21 A. That is correct, but they do</p> <p>22 contribute information that I utilize in</p> <p>23 terms of the whole to formulate my opinions.</p> <p>24 Q. Let me mark several of the</p>
<p style="text-align: right;">Page 19</p> <p>1 BY MR. ZELLERS:</p> <p>2 Q. What, then, is the difference</p> <p>3 between the references to your report and</p> <p>4 Exhibit B, which has a caption, Literature?</p> <p>5 A. The Exhibit B represents a</p> <p>6 larger set of documents, including scientific</p> <p>7 literature, technical reports, and so forth</p> <p>8 that I reviewed in preparation of my report</p> <p>9 and the formation of my opinions; but they</p> <p>10 did not contain information that I felt</p> <p>11 necessary to cite in my report.</p> <p>12 Q. The literature that you cite to</p> <p>13 as Appendix B of your report are materials</p> <p>14 that you reviewed but are not the materials</p> <p>15 that you're specifically relying on. The</p> <p>16 materials that you're specifically relying on</p> <p>17 are set forth in your references list; is</p> <p>18 that right?</p> <p>19 MS. O'DELL: Excuse me. Object</p> <p>20 to the form, misstates his testimony.</p> <p>21 A. My opinions are based on my</p> <p>22 total review of the literature as well as my</p> <p>23 training, my professional experience and many</p> <p>24 other factors.</p>	<p style="text-align: right;">Page 21</p> <p>1 attachments to your report as separate</p> <p>2 exhibits.</p> <p>3 (Carson Deposition Exhibit 3</p> <p>4 marked.)</p> <p>5 BY MR. ZELLERS:</p> <p>6 Q. Exhibit 3 is your curriculum</p> <p>7 vitae that was attached to your report; is</p> <p>8 that right?</p> <p>9 A. Yes.</p> <p>10 (Carson Deposition Exhibit 4</p> <p>11 marked.)</p> <p>12 BY MR. ZELLERS:</p> <p>13 Q. Exhibit 4 is a copy of your</p> <p>14 literature list that we just discussed that</p> <p>15 is in your report; is that right?</p> <p>16 A. Yes.</p> <p>17 MS. O'DELL: Thank you.</p> <p>18 BY MR. ZELLERS:</p> <p>19 Q. The one difference with</p> <p>20 Exhibit 4, your literature list that's</p> <p>21 attached to your report as Appendix B is not</p> <p>22 numbered. I've gone ahead and numbered the</p> <p>23 pages on Exhibit 4, your literature list, in</p> <p>24 case we want to refer to a specific page.</p>

1 Today, when I refer to
2 products, talc products, baby powder or
3 Shower to Shower, I'm referring to the baby
4 powder product manufactured by Johnson &
5 Johnson Consumer Products Inc. and the Shower
6 to Shower product formerly manufactured by
7 Johnson & Johnson Consumer Products Inc.

8 Do you understand that?

9 A. Yes.

10 Q. Is your report, Exhibit 2,
11 accurate?

12 A. I believe so.

13 Q. Do you believe it's complete?

14 A. In terms of its focus, yes.

15 Q. What do you mean in terms of
16 its focus?

17 A. It covers specific aspects of a
18 larger question, and regarding those specific
19 aspects, I believe it is complete.

20 Q. It covers the aspects of the
21 question that you intend to offer opinions
22 on, correct?

23 A. That is correct.

24 Q. What is the question that was

1 given to you by counsel for plaintiffs in
2 this litigation?

3 A. The question is do the -- does
4 the habitual use of talcum powder products
5 cause ovarian cancer.

6 Q. Were you given any other
7 questions to answer or opine on in this
8 litigation?

9 A. Not specifically.

10 Q. What do you understand habitual
11 use of talcum powder to refer to?

12 A. It means routine use, periodic
13 use.

14 Q. Over any period of time?

15 A. Over an extended period of
16 time.

17 Q. What is an extended period of
18 time?

19 A. Months or years.

20 Q. Any other definition that you
21 have of habitual use?

22 A. No.

23 Q. Today, in response to the
24 notice of deposition, you did bring the

1 binder of materials; is that right?

2 A. Yes.

3 Q. The binder of materials, did
4 you prepare that, or was it prepared for you?

5 A. Well, I uploaded documents to a
6 share file, and the plaintiffs' attorneys
7 were kind enough to print those for me and
8 assemble them in the binder.

9 Q. In addition, you have brought
10 with you a stack of eight or so additional
11 references that you have on the table in
12 front of you; is that right?

13 A. Yes.

14 Q. Are those materials that were
15 cited either as references in your report or
16 in the literature section of your report?

17 A. I think they're all included in
18 one or the other of those lists.

19 Q. Your testimony under oath is
20 that all of the additional materials you
21 brought here today are referred to either in
22 your reference list, which is -- begins at
23 page 11 of your report, or your literature
24 list, which we've marked as Exhibit 4 and is

1 Exhibit B to your report; is that right?

2 MS. O'DELL: Objection to the
3 form.

4 Go ahead.

5 A. There are a couple of new
6 articles here that were not available at the
7 time that I submitted my report, and I
8 believe the literature list was also created.

9 BY MR. ZELLERS:

10 Q. Were those new materials
11 provided to you by plaintiffs' counsel or are
12 those materials that you did some type of
13 literature search and found?

14 A. One of them was provided to me
15 by plaintiffs' counsel, but I was aware that
16 it was coming. And -- actually, two of them
17 were provided by plaintiffs' counsel.

18 Q. All right. The two additional
19 documents that were provided to you by
20 plaintiffs' counsel, can you show those to
21 me?

22 A. Okay. One is the Longo report.

23 Q. We will mark as
24 Deposition Exhibit 5 the Longo report dated

1 January 15th of 2009 [sic].
 2 (Carson Deposition Exhibit 5
 3 marked.)
 4 A. The other is the recent
 5 Fletcher, et al article.
 6 (Carson Deposition Exhibit 6
 7 marked.)
 8 BY MR. ZELLERS:
 9 Q. The Fletcher article dated
 10 January 3rd of 2019 we'll mark as Exhibit 6.
 11 This is an article from Reproductive
 12 Sciences; is that right?
 13 A. Yes. And I actually have a
 14 third.
 15 Q. All right. You have a third
 16 article that was provided to you by
 17 plaintiffs' counsel?
 18 A. Yes.
 19 (Carson Deposition Exhibit 7
 20 marked.)
 21 BY MR. ZELLERS:
 22 Q. Let's mark that as
 23 Deposition Exhibit 7. Can you tell us what
 24 article that is?

1 A. This is a meta-analysis.
 2 It's -- the title is Systematic Review and
 3 Meta-Analysis of the Association Between
 4 Perineal Use of Talc and Risk of Ovarian
 5 Cancer. The lead author is Mohamed Taher.
 6 Q. The Taher paper we have marked
 7 as Exhibit 7; is that right?
 8 A. Yes.
 9 Q. This is something that you were
 10 provided by plaintiffs' counsel; is that
 11 right?
 12 A. Yes.
 13 Q. Exhibit 6, Reproductive
 14 Sciences, are you familiar with that journal?
 15 A. I'm aware that it exists.
 16 Q. Do you review that journal on a
 17 regular basis as a part of your clinical and
 18 research activities?
 19 A. No, I don't.
 20 Q. Is Reproductive Sciences a
 21 peer-reviewed journal?
 22 A. I believe it is.
 23 Q. The Exhibit 6 has as a
 24 corresponding author, Dr. Saed, S-A-E-D, a

1 Ph.D.; is that right?
 2 A. Yes.
 3 Q. What additional articles have
 4 you brought here with you today separate and
 5 apart from your binder of materials?
 6 A. There's a copy of the IARC
 7 monographs preamble.
 8 Q. For what purpose did you bring
 9 that article?
 10 A. This discusses the general
 11 process that IARC uses in approaching a
 12 putative carcinogenic material.
 13 Q. That has previously been marked
 14 as Plaintiff Exhibit P-346 in another
 15 proceeding; is that right?
 16 A. I don't know.
 17 Q. Well, the document we're
 18 looking at has that exhibit sticker on it; is
 19 that right?
 20 A. It does.
 21 Q. What else have you brought here
 22 with you today?
 23 A. This is an article from
 24 The Lancet from 1952 titled Value of Modified

1 Starch as a Substitute for Talc, and the
 2 first author is J.D.P. Graham.
 3 Q. Why did you bring that article?
 4 A. This is an older article that
 5 discusses the suitability of substituting
 6 cornstarch materials for talc due to
 7 perceived issues with talc.
 8 Q. Is this an article that you had
 9 cited previously, either in your references
 10 or your list of literature?
 11 A. I did not cite it in my report.
 12 I don't know -- I don't recall if it's in the
 13 literature list or not.
 14 (Carson Deposition Exhibit 8
 15 marked.)
 16 BY MR. ZELLERS:
 17 Q. Why did you decide to bring
 18 that with you here today?
 19 A. It is in the literature list.
 20 I ran across it last night, and
 21 I thought I might need to refer to it during
 22 the deposition.
 23 Q. What other documents or
 24 materials have you brought other than your

1 binder of materials?

2 A. I have here a copy of the
3 recent Canadian position on the safety of
4 talcum powder and its relationship to ovarian
5 cancer.

6 Q. When did you review that
7 document?

8 A. A couple weeks ago, I think.

9 Q. Is that a document that you
10 were provided by plaintiffs' counsel?

11 A. It was.

12 Q. Can I see the document, please?
13 We'll mark the draft screening assessment
14 from Health Canada dated December 18th of
15 2018 as Exhibit 9.

16 (Carson Deposition Exhibit 9
17 marked.)

18 BY MR. ZELLERS:

19 Q. Any other documents?

20 A. I have a copy of the letter
21 from the FDA from April 1st, 2014 responding
22 to positions -- petitions for labeling.

23 Q. This is a letter that has a
24 stamp on it on the first page, April 1st,

1 2014, from -- or strike that -- to
2 Dr. Epstein from the FDA; is that right?

3 A. Yes.

4 Q. Let's mark that as Exhibit 10.
5 (Carson Deposition Exhibit 10
6 marked.)

7 BY MR. ZELLERS:

8 Q. What else?

9 A. I have an article authored by
10 A.M. Blount which is titled Amphibole Content
11 of Cosmetic and Pharmaceutical Talcs that was
12 published in Environmental Health
13 Perspectives in 1991.

14 Q. Is that a journal that you
15 review on a regular basis as part of either
16 your clinical practice or your research
17 activities?

18 A. That one I do look at pretty
19 much.

20 Q. Is this an article you were
21 aware of back in 1991?

22 A. No. At least I don't recall.

23 Q. Is it fair that your review of
24 this literature, the literature relating to

1 talcum powder and ovarian cancer, is
2 something that you undertook when you were
3 retained by plaintiffs' counsel and asked to
4 address the question they gave to you?

5 A. Yes, it is.

6 Q. We will mark the article by
7 Blount as Exhibit 11.

8 (Carson Deposition Exhibit 11
9 marked.)

10 BY MR. ZELLERS:

11 Q. And you have one more; is that
12 right?

13 A. Yes, one more, which is -- this
14 is an article from the American Journal of
15 Obstetrics and Gynecology from 1974 titled
16 The Ovarian Mesothelioma. It's authored by
17 Parmley and Woodruff.

18 Q. We'll mark that as Exhibit 12.
19 (Carson Deposition Exhibit 12
20 marked.)

21 BY MR. ZELLERS:

22 Q. Exhibit 12, is this an article
23 that was cited previously by you in either
24 your references or your literature list?

1 A. Yes.

2 Q. For what -- strike that.

3 Is this a document that you
4 chose to bring today or were you provided it
5 by plaintiffs' counsel?

6 A. This is another one I ran
7 across last night and decided to bring along
8 to the depo.

9 Q. Same questions with respect to
10 the Blount article, Exhibit 11: Is this an
11 article you cite in your references or
12 literature?

13 A. In the literature, yes.

14 Q. For what purpose have you
15 brought this with you today?

16 A. I thought I might want to refer
17 to it in response to questions here.

18 Q. Exhibit 10, the letter from the
19 FDA to Dr. Epstein, April of 2014, for what
20 purpose have you brought that here with you
21 today?

22 A. I thought I might want to refer
23 to it in response to questioning.

24 Q. The documents that you have

1 brought here with you today are documents
2 that you wanted to have available to try to
3 respond to the questions that I may ask you?

4 A. Yes.

5 Q. These documents you all
6 believe -- strike that.

7 The documents that you've
8 identified and you've brought with you --
9 have brought with you today, you believe
10 those are supportive of the opinions that you
11 are rendering in this matter; is that right?

12 A. Yes.

13 Q. The documents on your
14 literature list, what we have marked as
15 Exhibit 4, are those documents that were
16 provided to you by plaintiffs' counsel?

17 A. Some were.

18 Q. The documents on this list that
19 were not provided by plaintiffs' counsel, did
20 you find those through a literature search?

21 A. Yes.

22 Q. Are you able to distinguish for
23 us which documents on your literature list,
24 Exhibit 4, came from plaintiffs' counsel and

1 which items on the literature list you came
2 up with?

3 A. To some extent.

4 Q. So if we went through item by
5 item, you believe you could distinguish
6 between what was provided to you by
7 plaintiffs and what you found on your own?

8 A. For some, but not all of them.

9 Q. Have you reviewed all of the
10 materials that are listed on your literature
11 list?

12 A. I have reviewed all of them,
13 yes.

14 Q. Have you reviewed all of the
15 materials that are on your reference list?

16 A. Yes.

17 Q. The materials on your reference
18 list, is it the same that some were provided
19 to you by plaintiffs' counsel and some you
20 found on your own?

21 A. I think there may be one or two
22 references that I didn't have before I saw
23 them in the share file that may have been
24 provided by plaintiffs' counsel, but I

1 wouldn't be able to tell you for sure. I'm
2 sure I ran across these in my own literature
3 search.

4 Q. Deposition Exhibit 13, we will
5 mark the thumb drive that plaintiffs' counsel
6 has brought here today.

7 (Carson Deposition Exhibit 13
8 marked.)

9 BY MR. ZELLERS:

10 Q. Do you, Dr. Carson, have an
11 understanding of what's on the thumb drive
12 we've marked as Exhibit 13?

13 A. My understanding is this is
14 copies of the documents on the literature
15 list.

16 Q. When were you first retained by
17 anyone regarding the talc/ovarian cancer
18 litigation?

19 A. In October of 2018.

20 Q. Who contacted you?

21 A. I was contacted by an attorney
22 named Russ Abney.

23 Q. Who is Mr. Abney, if you know?

24 A. Mr. Abney is a lawyer who used

1 to work in the Houston area and with whom I
2 had some dealings years ago; and since that
3 time he has become involved in this talc
4 litigation in some way, was aware of me as a
5 potential expert witness, and contacted me
6 regarding my interest and availability.

7 Q. What matters have you worked on
8 with Mr. Abney in the past?

9 A. I think it would have been back
10 in the 1990s, and I frankly don't recall what
11 cases we worked on, but there were one or
12 maybe two cases.

13 Q. When in October of 2018 were
14 you contacted by Mr. Abney?

15 MS. O'DELL: Object to the
16 form.

17 A. I believe it was either the
18 14th or 15th of October.

19 BY MR. ZELLERS:

20 Q. How do you remember with that
21 precision?

22 A. I have an e-mail that relates
23 to a phone call which was our initial
24 contact.

<p style="text-align: right;">Page 38</p> <p>1 Q. Mr. Abney at some point asked</p> <p>2 you to address the question that you told us</p> <p>3 before: Does the habitual use of talcum</p> <p>4 powder cause ovarian cancer?</p> <p>5 Is that right?</p> <p>6 MS. O'DELL: Object to the</p> <p>7 form.</p> <p>8 A. Well, he talked to me generally</p> <p>9 about the case that was proceeding, and I</p> <p>10 discussed with him what my understanding of</p> <p>11 those things was and what the kind of</p> <p>12 opinions I would be able to render would be.</p> <p>13 And he suggested that he set up a meeting</p> <p>14 between me and members of plaintiffs'</p> <p>15 counsel.</p> <p>16 BY MR. ZELLERS:</p> <p>17 Q. When Mr. Abney called you</p> <p>18 middle of October of 2018, talcum powder and</p> <p>19 any relationship or association that it may</p> <p>20 have to ovarian cancer had not been a focus</p> <p>21 of your research or study; is that right?</p> <p>22 A. That's right.</p> <p>23 Q. It had not been a part of your</p> <p>24 clinical practice, right?</p>	<p style="text-align: right;">Page 40</p> <p>1 doing a review? What does that mean?</p> <p>2 A. Well, I felt that I was hired</p> <p>3 as a witness at that point and that's when I</p> <p>4 would begin my billable hours on this case.</p> <p>5 Q. When was that? Sometime in</p> <p>6 later October of -- late October of 2018?</p> <p>7 A. It was within a few days after</p> <p>8 our first meeting, still in October.</p> <p>9 Q. What did you do to answer the</p> <p>10 question? What was your methodology?</p> <p>11 A. Well, initially I decided to do</p> <p>12 a general literature search on the question</p> <p>13 to see what research had been performed, what</p> <p>14 reports had been written, what the quality of</p> <p>15 that research was.</p> <p>16 Q. When did you start that?</p> <p>17 A. Immediately. I was curious.</p> <p>18 I began to assemble the</p> <p>19 available literature and review it on a</p> <p>20 piecemeal basis through the subsequent time</p> <p>21 period; the next couple of weeks I reviewed a</p> <p>22 lot of it.</p> <p>23 Q. What did you search for when</p> <p>24 you did this general literature search?</p>
<p style="text-align: right;">Page 39</p> <p>1 A. That's correct.</p> <p>2 Q. When did you meet with the</p> <p>3 larger group of plaintiffs' counsel?</p> <p>4 A. I believe we had a telephone</p> <p>5 meeting on the 16th of October. I'm not</p> <p>6 sure. I have to --</p> <p>7 Q. That's -- right now I just want</p> <p>8 estimates.</p> <p>9 A. Okay.</p> <p>10 Q. And so I don't -- as long as</p> <p>11 you're reasonably comfortable that it was in</p> <p>12 that time frame.</p> <p>13 A. It was mid October.</p> <p>14 Q. That's fine.</p> <p>15 When were you asked the</p> <p>16 question that the plaintiffs' lawyers wanted</p> <p>17 you to try to answer in this litigation?</p> <p>18 A. Well, after the meeting we</p> <p>19 parted ways and then made contact again a few</p> <p>20 days later, and I was told that they were</p> <p>21 interested in me going ahead and doing a</p> <p>22 review and starting to establish opinions.</p> <p>23 Q. What do you mean by they</p> <p>24 authorized you or were comfortable with you</p>	<p style="text-align: right;">Page 41</p> <p>1 A. I searched under various search</p> <p>2 terms, including "talc," including "ovarian</p> <p>3 cancer," the relationship between the two.</p> <p>4 As I became more familiar with the</p> <p>5 literature, I expanded that search into other</p> <p>6 topics.</p> <p>7 As I became -- I was already</p> <p>8 aware of issues related to the inclusion of</p> <p>9 asbestos in talc deposits, and so I expanded</p> <p>10 my search into that part of the literature</p> <p>11 that relates to asbestos in talc or asbestos</p> <p>12 in ovarian cancer.</p> <p>13 As I felt my opinions would</p> <p>14 need to extend into cancer and carcinogenesis</p> <p>15 in general, I did some search into ovarian</p> <p>16 cancer specifically and general</p> <p>17 carcinogenesis to see what the current state</p> <p>18 of the art was regarding that in the</p> <p>19 literature.</p> <p>20 I looked at some issues of</p> <p>21 mining practices.</p> <p>22 I looked at the Johnson &</p> <p>23 Johnson website. There's a webpage regarding</p> <p>24 talc and ovarian cancer that I looked at.</p>

<p style="text-align: right;">Page 42</p> <p>1 I looked through old notes and</p> <p>2 lecture files that I had for information that</p> <p>3 I've used or accessed previously in my</p> <p>4 professional capacity for information that</p> <p>5 was pertinent.</p> <p>6 Just a very dendritic kind of</p> <p>7 extensive search.</p> <p>8 Q. You reviewed these materials</p> <p>9 that you have told us about and then did you</p> <p>10 prepare your report?</p> <p>11 A. At that point I -- well, the</p> <p>12 literature review took several stages.</p> <p>13 Typically when you perform a review like</p> <p>14 this, you end up with a -- I do a very</p> <p>15 general sort of approach to a review, so I</p> <p>16 get much more than will be pertinent to my</p> <p>17 review eventually.</p> <p>18 I find that a valuable approach</p> <p>19 because it allows me to find things I</p> <p>20 wouldn't otherwise find or look for or know</p> <p>21 to look for.</p> <p>22 And then I'm able to cull</p> <p>23 through that information and discard pieces</p> <p>24 of the search materials that are not relevant</p>	<p style="text-align: right;">Page 44</p> <p>1 review of draft versions of my report and</p> <p>2 comments, in particular --</p> <p>3 Q. Don't tell me about the</p> <p>4 comments.</p> <p>5 A. Okay.</p> <p>6 Q. I don't want to know what the</p> <p>7 lawyers may have told you.</p> <p>8 Did the comments come from the</p> <p>9 lawyers for plaintiffs or did they come from</p> <p>10 other people?</p> <p>11 A. They came from the lawyers.</p> <p>12 They also came from a few of my colleagues.</p> <p>13 Q. Did you share your report with</p> <p>14 some of your colleagues?</p> <p>15 A. I let a few people read it and</p> <p>16 I talked to them about it.</p> <p>17 Q. Are the opinions your opinions?</p> <p>18 A. Yes, they are.</p> <p>19 Q. Have you told me, you know,</p> <p>20 generally what you have done to formulate</p> <p>21 your opinions in this matter?</p> <p>22 A. Yes, I think so.</p> <p>23 Q. You did all of this over a</p> <p>24 30-day period; is that right?</p>
<p style="text-align: right;">Page 43</p> <p>1 or interesting to me and then refine my</p> <p>2 search and redo it, extending it into</p> <p>3 different areas that have now become</p> <p>4 pertinent in my opinion, until I satisfy</p> <p>5 myself that I have pretty much covered the</p> <p>6 waterfront so to speak in terms of a</p> <p>7 literature review.</p> <p>8 Q. You did your literature review.</p> <p>9 You reviewed the Johnson & Johnson website</p> <p>10 and the other materials that you have told us</p> <p>11 about.</p> <p>12 Did you then formulate your</p> <p>13 opinions and set them down in your report</p> <p>14 which we marked as Exhibit 2?</p> <p>15 A. I did. I began writing as I</p> <p>16 reviewed the literature and continued to take</p> <p>17 notes which, through a continuous editing</p> <p>18 process, eventually became my report.</p> <p>19 Q. Did you prepare your report?</p> <p>20 A. I did.</p> <p>21 Q. Did anyone assist you in the</p> <p>22 preparation of your report?</p> <p>23 A. No one assisted me in the</p> <p>24 preparation of my report. I did receive</p>	<p style="text-align: right;">Page 45</p> <p>1 A. Yes.</p> <p>2 Q. All right. You have no</p> <p>3 invoices, correct?</p> <p>4 A. That's correct.</p> <p>5 Q. Is it typical that you'll work</p> <p>6 on a matter for some number of months and not</p> <p>7 generate any invoices?</p> <p>8 A. Yes.</p> <p>9 Q. You are billing your time at</p> <p>10 what rate?</p> <p>11 A. \$450 per hour.</p> <p>12 Q. Can you estimate for us the</p> <p>13 number of hours that you have spent doing</p> <p>14 your literature review, formulating your</p> <p>15 opinions, and writing your report?</p> <p>16 A. There's still some tallying I</p> <p>17 need to do from my calendar, but it's between</p> <p>18 150 and 180 hours.</p> <p>19 Q. Does that include your meetings</p> <p>20 and communications with plaintiffs' counsel?</p> <p>21 A. Yes, that's up until today.</p> <p>22 Q. Other than meeting with</p> <p>23 Mr. Abney or talking with Mr. Abney -- did</p> <p>24 you ever meet with Mr. Abney face-to-face?</p>

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1 A. No.

2 Q. What other plaintiff lawyers

3 have you met with or talked with as part of

4 your formulating your opinions and doing your

5 literature review?

6 A. We've had a number of

7 conference calls where there were several of

8 these attorneys' colleagues on the line, but

9 in terms of in-person meetings, those have

10 been with Ms. O'Dell and Ms. Thompson,

11 Dr. Thompson.

12 Q. How many meetings have you had

13 with Ms. O'Dell?

14 A. Three.

15 Q. How many meetings have you had

16 with Dr. Thompson?

17 A. Three.

18 Q. Did you know Dr. Thompson

19 before you were retained in this matter?

20 A. I did not.

21 Q. Any other plaintiff lawyers in

22 this litigation that you are aware of --

23 strike that.

24 Any other plaintiff lawyers in

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1 this matter that you've had communications

2 with other than what you have told us?

3 A. No.

4 Q. Do you have any social

5 relationship with any of the plaintiffs'

6 counsel?

7 A. No.

8 Q. Your relationship with

9 Dr. Thompson is just the three meetings that

10 you have been involved in with her?

11 A. Well, we've exchanged e-mail

12 communications, but other than that, no.

13 Q. Have you met with or talked

14 with any other expert witness for plaintiffs?

15 A. No, I have not.

16 Q. Do you know who Thomas Dydek

17 is?

18 A. Yes.

19 Q. Who is Thomas Dydek?

20 A. He is a toxicologist.

21 Q. Where does he practice?

22 A. I don't recall.

23 Q. Have you had any discussions

24 with Dr. Dydek?

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1 A. I have not had any discussions

2 with Dr. Dydek. We may have met previously,

3 but I don't recall.

4 Q. Any previous meeting with

5 Dr. Dydek, did it relate to this litigation?

6 A. No.

7 Q. Did it relate to expert witness

8 work that you were doing?

9 A. No.

10 Q. Do you know what the

11 relationship is, if any, between Dr. Thompson

12 and Dr. Dydek?

13 A. I don't know of any

14 relationship outside of his work as an expert

15 witness in related litigation.

16 Q. Dr. Crowley, do you know

17 Michael Crowley?

18 A. I know of Dr. Crowley.

19 Q. Did you know of Dr. Crowley

20 before you were retained in the talcum powder

21 litigation?

22 A. No.

23 Q. Have you ever met with

24 Dr. Crowley?

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1 A. I have not.

2 Q. Ever talked with Dr. Crowley?

3 A. I have not.

4 Q. You reviewed his report as part

5 of your review in this matter; is that right?

6 A. That's correct.

7 Q. Do you know who any of the

8 other experts are in this litigation for

9 plaintiffs?

10 A. Well, I know there are a number

11 of people who have generated reports that I

12 have also reviewed.

13 Q. What reports have you reviewed

14 from plaintiffs' other experts?

15 A. Well, I've reviewed several

16 reports from Dr. Longo, who's done work on

17 the presence of asbestos in talc products and

18 related things. I think he's the only other

19 expert that I'm aware of at this point.

20 Q. Well, you're aware of

21 Dr. Crowley?

22 A. Well, Dr. Crowley, Dr. Longo,

23 and Dr. Dydek that you mentioned before.

24 Q. Have you reviewed any reports

1 or transcripts from Dr. Dydek?
 2 A. Yes, I reviewed an expert
 3 report that he provided before I got involved
 4 in this case.
 5 Q. Did you review that report
 6 before you prepared your report?
 7 A. Yes.
 8 Q. Did you review Dr. Crowley's
 9 report before you prepared your report?
 10 A. Yes.
 11 Q. And you reviewed Dr. Longo's
 12 report before you prepared your report; is
 13 that right?
 14 A. I've reviewed one report.
 15 There was another one that became available
 16 after.
 17 Q. The second report is what you
 18 brought here with you today and we marked as
 19 Exhibit 5; is that right?
 20 A. Yes.
 21 Q. Any other plaintiff experts
 22 that you're aware of?
 23 A. Not that I can think of, no.
 24 Q. Any other reports from

1 plaintiffs' experts that you have reviewed?
 2 A. Well, there's a -- there is an
 3 article that's been submitted for publication
 4 which I consider a piece of the scientific
 5 literature. You mentioned Dr. Saed earlier,
 6 and I know that he has a relationship with
 7 this case as well.
 8 Q. What is his relationship with
 9 this case, Dr. Saed?
 10 A. He's provided some work at the
 11 request of the attorneys here.
 12 Q. Have you reviewed that work?
 13 A. That's the subject of several
 14 articles he's published previously, he and
 15 his colleagues, as well as the additional one
 16 that I brought today.
 17 Q. Other than the articles that
 18 you have listed on your reference and
 19 literature list and the Saed article that you
 20 brought with you today, are you aware of any
 21 other work that Dr. Saed has done in this
 22 matter?
 23 A. No.
 24 Q. Any other plaintiff experts

1 that you're aware of?
 2 A. No.
 3 Q. Are you aware of any of the
 4 experts for defendants in the talcum powder
 5 litigation?
 6 A. No.
 7 Q. Have you reviewed any reports
 8 from any of the experts in the talcum powder
 9 litigation?
 10 A. I have not.
 11 Q. Have you reviewed any of the
 12 transcripts of defense experts in the talcum
 13 powder litigation?
 14 A. I've reviewed some deposition
 15 transcripts of various witnesses.
 16 Q. Those witnesses are all listed
 17 in either your references or your literature;
 18 is that right?
 19 A. Yes.
 20 Q. Did you review the entire
 21 transcripts of the witnesses that you've
 22 identified?
 23 A. I think for the most part I
 24 would say yes.

1 Q. Did you review the exhibits to
 2 those depositions?
 3 A. Yes. If they were provided to
 4 me, I did, yes.
 5 Q. Did you believe that it was
 6 your job to do an independent assessment as
 7 to whether or not the habitual use of talcum
 8 powder causes or can cause ovarian cancer?
 9 MS. O'DELL: Object to the
 10 form.
 11 A. Could you repeat the question,
 12 please.
 13 BY MR. ZELLERS:
 14 Q. Sure.
 15 Plaintiffs asked you to --
 16 strike that.
 17 Plaintiffs' counsel asked you
 18 to answer that question; is that right?
 19 A. Yes.
 20 Q. You understood that they were
 21 looking to develop an association or a causal
 22 relationship between the habitual use of
 23 talcum powder and ovarian cancer, correct?
 24 A. Yes.

1 MS. O'DELL: Object to the
2 form.
3 Excuse me, I'm sorry,
4 gentlemen. Give me just one second to
5 object if I need to.

6 THE WITNESS: Sure.

7 MS. O'DELL: Thank you.

8 BY MR. ZELLERS:

9 Q. Did you consider the literature
10 and the sources that refuted that association
11 or causal relationship?

12 A. I tried to consider all the
13 available literature.

14 Q. When you wrote your report
15 setting forth your opinions, did you set
16 forth the sources that refuted the
17 propositions you were making?

18 A. I cited several sources that on
19 the surface might seem to refute my opinions.

20 Q. And you believe that is
21 contained in your report which we marked as
22 Exhibit 2; is that right?

23 A. Yes.

24 Q. Have you been involved in any

1 other talcum powder litigation other than
2 this talc MDL matter that Mr. Abney talked to
3 you about?

4 A. No, I haven't.

5 Q. In the 30 to 35 occasions that
6 you've testified in the past, have any of
7 those been on issues relating to talcum
8 powder and any association between talcum
9 powder and ovarian cancer?

10 A. No.

11 Q. You are not an expert in
12 asbestos, correct?

13 MS. O'DELL: Object to the
14 form.

15 A. I'm an occupational medicine
16 physician, and I have a significant amount of
17 awareness and training regarding asbestos as
18 it relates to occupational exposures and
19 general environmental exposures, but I don't
20 consider myself an asbestos expert.

21 BY MR. ZELLERS:

22 Q. What percentage of your time do
23 you spend working as a consultant? And I'm
24 talking about your professional time.

1 A. Probably 5%.

2 Q. What percent of your income
3 comes from the work that you do as a
4 consultant?

5 A. Of course it varies quite a bit
6 from moment to moment, but it would be less
7 than 10%.

8 Q. Have you ever testified at
9 trial?

10 A. Yes.

11 Q. On how many occasions?

12 A. Probably ten.

13 Q. The 30 to 35 depositions that
14 you've given previously, those have been in
15 the context of you providing litigation
16 consulting services; is that right?

17 A. In terms of expert testimony,
18 yes.

19 Q. The trial appearances that
20 you've made, are those also in your capacity
21 as an expert witness?

22 A. Yes.

23 Q. Have you been involved in other
24 litigations?

1 A. Yes.

2 Q. What other litigations have you
3 been involved in as an expert?

4 A. Well, I've been asked to
5 provide opinions and testify in a number of
6 cases, most of which involved personal injury
7 in the occupational setting or environmental
8 exposures.

9 Q. Has the majority of your expert
10 work in the occupational setting and for
11 environmental exposures been on behalf of
12 plaintiffs?

13 A. No, it's been split about
14 50/50, plaintiff and defense.

15 Q. Have you ever been retained in
16 a case involving cosmetic products?

17 A. No.

18 Q. Your curriculum vitae that we
19 marked as Exhibit 3, is it correct and up to
20 date?

21 A. It was up to date at the time
22 of submission of my report in the end of
23 2018.

24 Q. What additions need to be made

<p style="text-align: right;">Page 58</p> <p>1 or corrections need to be made to your CV, 2 Exhibit 3, to bring it up to date? 3 A. Well, I've terminated a 4 relationship with the University of Texas 5 Medical Branch in Galveston where I was 6 their -- the medical director of their 7 Employee Health Services Clinic. I continue 8 to be -- serve as an assistant clinical 9 professor of preventive medicine and family 10 medicine at that institution. 11 I have terminated my 12 relationship with the Enbridge Corporation as 13 their medical director. 14 The Spectra Energy entry, which 15 is about the seventh on the list of 16 professional activities, is also terminated 17 as that was a company that was merged and 18 became Enbridge. 19 Q. Any other corrections or 20 updates to your curriculum vitae that we've 21 marked as Exhibit 3? 22 A. No. 23 Q. Why are you no longer serving 24 as medical director, Employee Health Services</p>	<p style="text-align: right;">Page 60</p> <p>1 is that right? 2 A. Yes. 3 Q. What percentage of your time is 4 spent in the clinical practice of medicine? 5 A. Currently I see patients 6 one-half day a week and work as a supervisor 7 of the occupational medicine residents for 8 additional time during the week, so clinical 9 activities would be about probably 12 hours a 10 week. 11 Q. Do you see or treat women for 12 gynecologic cancer? 13 A. I do not. 14 Q. You have never worked for a 15 company that manufactures cosmetic products, 16 correct? 17 A. That's correct. 18 Q. You're not a gynecologist or an 19 oncologist, correct? 20 A. That's correct. 21 Q. You're not a cancer biologist? 22 MS. O'DELL: Object to the 23 form. 24 A. That's correct.</p>
<p style="text-align: right;">Page 59</p> <p>1 with the University of Texas? 2 MS. O'DELL: Objection to form. 3 A. That was a contract that I had 4 through the University of Texas Houston 5 College of Nursing that provided those 6 services to UTMB, and UTMB decided to make a 7 change and go with another contractor. 8 BY MR. ZELLERS: 9 Q. Why are you no longer serving 10 as medical director for Spectra Energy 11 Corporation and Enbridge Corporation? 12 A. Well, Spectra Energy no longer 13 exists; it became Enbridge Corporation. And 14 in October of 2018, I determined that I did 15 not -- I no longer had sufficient time to 16 provide that service. 17 Q. Your undergraduate degree was 18 in biologic sciences with a concentration in 19 engineering; is that right? 20 A. Yes. 21 Q. You received a Ph.D. in 22 toxicology; is that right? 23 A. Yes. 24 Q. And then later an M.D. degree;</p>	<p style="text-align: right;">Page 61</p> <p>1 BY MR. ZELLERS: 2 Q. You are not a geologist, 3 mineralogist or microscopist? 4 A. That's correct. 5 Q. You're not an epidemiologist? 6 A. Well, I may be considered an 7 epidemiologist simply by my appointment as an 8 associate professor in the Department of 9 Epidemiology at the School of Public Health 10 here in Houston. 11 Q. Do you have any professional 12 education in the field -- well, strike that. 13 Have you ever published or 14 conducted a meta-analysis? 15 A. I have conducted meta-analyses. 16 I've not published them. 17 Q. You did not do any type of 18 fellowship in epidemiology, correct? 19 A. That's correct. 20 Q. You're not board certified in 21 epidemiology; is that right? 22 A. I don't believe there is a 23 board certification in epidemiology. 24 Q. You're not a biostatistician or</p>

1 a pulmonologist?
 2 A. That's correct.
 3 Q. You're not a material
 4 scientist?
 5 A. That's correct.
 6 Q. Nor are you a pathologist?
 7 A. Correct.
 8 Q. You've never been involved in
 9 any pathological exam or research relating to
 10 ovarian cancer; is that right?
 11 MS. O'DELL: Object to the
 12 form.
 13 A. I'm not sure exactly what you
 14 mean by your question.
 15 BY MR. ZELLERS:
 16 Q. Sure. Let me withdraw that.
 17 You've never been involved in
 18 terms of the research relating to ovarian
 19 cancer, correct?
 20 A. Not specifically, no.
 21 Q. You've never authored any
 22 literature or publications relating to talcum
 23 powder?
 24 A. No.

1 Q. Or relating to ovarian cancer,
 2 correct?
 3 A. No.
 4 Q. Okay. What journals -- well,
 5 strike that.
 6 You have never published on
 7 fragrance chemicals; is that right?
 8 MS. O'DELL: Object to the
 9 form.
 10 A. That's correct.
 11 BY MR. ZELLERS:
 12 Q. Never done any research on
 13 fragrance chemicals, correct?
 14 A. I've done some work with
 15 fragrance chemicals and health effects that
 16 are associated with them, but I have not -- I
 17 would not classify that as research or
 18 publication.
 19 Q. You had no opinions regarding
 20 talcum powder or any of its constituent
 21 components before getting involved in this
 22 litigation; is that right?
 23 MS. O'DELL: Object to the
 24 form.

1 A. I think I had opinions about
 2 talcum powder and its constituents, but if
 3 you could be more specific, I might be able
 4 to give you a more specific answer.
 5 BY MR. ZELLERS:
 6 Q. Did you ever, before getting
 7 involved in this litigation in October of
 8 2018, do research -- strike that.
 9 You've never published on
 10 talcum powder, correct?
 11 A. That's correct.
 12 Q. You have never published on the
 13 constituent components of talcum powder,
 14 correct?
 15 A. That may not be the case. I've
 16 done work in some other minerals which have
 17 resulted in publications, for example,
 18 vermiculite, which have touched on the issues
 19 of asbestos, association with talc,
 20 association with other minerals, but never
 21 specifically regarding talc.
 22 Q. Are those publications on your
 23 CV?
 24 A. They are.

1 Q. That we marked as Exhibit 3?
 2 A. Yes.
 3 Q. Okay. Have you ever
 4 communicated with the FDA regarding talcum
 5 powder?
 6 A. I've not.
 7 Q. Have you ever communicated with
 8 Health Canada regarding talcum powder?
 9 A. No.
 10 Q. When did you first start
 11 preparing your report which we've marked as
 12 Exhibit 2?
 13 A. Well, I began a literature
 14 review immediately after talking to
 15 Mr. Abney.
 16 Q. My question, I guess, is: When
 17 did you start writing your report?
 18 A. Well, technically I started
 19 writing my report after I was retained by
 20 plaintiffs' counsel.
 21 Q. Late October, early
 22 November 2018?
 23 MS. O'DELL: Object to the
 24 form, misstates his prior testimony.

<p style="text-align: right;">Page 66</p> <p>1 A. In October of 2018.</p> <p>2 BY MR. ZELLERS:</p> <p>3 Q. Have you reviewed any of the</p> <p>4 deposition transcripts of any of the experts</p> <p>5 that have been deposed in this litigation?</p> <p>6 A. Yes.</p> <p>7 Q. What deposition transcripts of</p> <p>8 experts have you reviewed?</p> <p>9 A. Oh, of experts? No, I have not</p> <p>10 reviewed -- well, I've reviewed -- I've</p> <p>11 reviewed expert depositions, but I don't know</p> <p>12 what case they were deposed in, but it</p> <p>13 relates to talcum powder and ovarian cancer</p> <p>14 issue.</p> <p>15 Q. What expert depositions have</p> <p>16 you reviewed?</p> <p>17 A. They're all cited in the</p> <p>18 literature exhibit.</p> <p>19 Q. All of the deposition</p> <p>20 transcripts that you've reviewed are cited in</p> <p>21 Exhibit 4?</p> <p>22 A. I think any of the transcripts</p> <p>23 that I review are -- reviewed are probably</p> <p>24 included in here.</p>	<p style="text-align: right;">Page 68</p> <p>1 and bolts of what goes on legally in this</p> <p>2 case. I know there are multiple lawsuits,</p> <p>3 and I'm not sure which ones those -- these</p> <p>4 are pertinent to.</p> <p>5 BY MR. ZELLERS:</p> <p>6 Q. My question is a little</p> <p>7 different and I hope pretty simple: In</p> <p>8 addition to the depositions, transcripts and</p> <p>9 reports that you have listed on pages 27 and</p> <p>10 28 of Exhibit 4, your literature list, are</p> <p>11 there any additional depositions or</p> <p>12 transcripts that you've reviewed?</p> <p>13 A. Pardon me for a moment while I</p> <p>14 review this.</p> <p>15 (Document review.)</p> <p>16 A. No, I'm not aware that there</p> <p>17 are.</p> <p>18 BY MR. ZELLERS:</p> <p>19 Q. Your testimony earlier was that</p> <p>20 you have reviewed each of those depositions</p> <p>21 in their entirety; is that right?</p> <p>22 A. Yes.</p> <p>23 Q. You have also reviewed the</p> <p>24 exhibits to those depositions; is that right?</p>
<p style="text-align: right;">Page 67</p> <p>1 Q. Are you aware of reviewing any</p> <p>2 transcripts that you did not include in your</p> <p>3 literature statement?</p> <p>4 A. I'm not aware, but I can't tell</p> <p>5 you as I'm sitting here right now whether all</p> <p>6 of those are included in this literature</p> <p>7 statement or not.</p> <p>8 Q. You -- looking at page --</p> <p>9 MS. O'DELL: I'm sorry. Go</p> <p>10 ahead.</p> <p>11 BY MR. ZELLERS:</p> <p>12 Q. Are there any that you believe</p> <p>13 you have reviewed that are not included in</p> <p>14 the literature statement?</p> <p>15 A. Well, let me just see here.</p> <p>16 There are --</p> <p>17 MS. O'DELL: I think they're at</p> <p>18 the end, Dr. Carson.</p> <p>19 THE WITNESS: At the very end.</p> <p>20 A. Beginning on page 27 is a list</p> <p>21 of the depositions, transcripts and reports</p> <p>22 that I've reviewed, which include some of the</p> <p>23 expert witnesses, but again, I would have to</p> <p>24 say I'm -- I'm sort of unaware of the nuts</p>	<p style="text-align: right;">Page 69</p> <p>1 A. If they were made available to</p> <p>2 me, I've looked at all those exhibits as</p> <p>3 well.</p> <p>4 Q. On page 27 of Exhibit 4, who is</p> <p>5 Annie Yessaian?</p> <p>6 A. On page 24?</p> <p>7 Q. Strike that. I'm sorry. On</p> <p>8 page 27 of Exhibit 4 --</p> <p>9 A. I see.</p> <p>10 Q. -- at the bottom, who is Annie</p> <p>11 Yessaian?</p> <p>12 A. I don't recall.</p> <p>13 Q. You reviewed her entire</p> <p>14 transcript and you don't recall who she is?</p> <p>15 A. I don't.</p> <p>16 Q. Well, go to the next page. Who</p> <p>17 is Pat Downey?</p> <p>18 A. I believe Pat Downey is an</p> <p>19 operative of the Imerys company.</p> <p>20 Q. Do you know what Mr. Downey's</p> <p>21 position is?</p> <p>22 A. It's a supervisory position</p> <p>23 regarding -- regarding quality of the talc</p> <p>24 product.</p>

1 Q. Who is John Hopkins?
 2 A. John Hopkins is an official, I
 3 believe, of -- I'm not sure -- of Johnson &
 4 Johnson, I believe, who has some oversight of
 5 talc quality as well.
 6 Q. Susan Nicholson, who is she?
 7 A. I don't recall.
 8 Q. Who is Julie Pier?
 9 A. Julie Pier is another scientist
 10 who works for Imerys, who is responsible for
 11 testing and quality.
 12 Q. In your clinical and academic
 13 practice, do you typically rely upon
 14 depositions of company witnesses or experts?
 15 MS. O'DELL: Object to the
 16 form.
 17 A. If there's pertinent
 18 information in there that leads me to other
 19 areas or helps me formulate my opinions, then
 20 yes.
 21 BY MR. ZELLERS:
 22 Q. In the papers and publications
 23 that you have identified in your curriculum
 24 vitae, Exhibit 3, do you ever recall citing

1 to company witness deposition testimony?
 2 A. I don't typically cite
 3 deposition testimonies in published papers.
 4 Q. You cite to various company
 5 documents. This is on pages 29 to 30 of
 6 Exhibit 4, your list of literature; is that
 7 right?
 8 A. Yes.
 9 Q. Did you rely on these documents
 10 in formulating your opinions?
 11 A. Yes.
 12 Q. Were these documents selected
 13 for you by plaintiffs' counsel?
 14 A. Yes, they were.
 15 Q. Are you able to identify what
 16 each of the documents are?
 17 MS. O'DELL: Based on the Bates
 18 number?
 19 MR. ZELLERS: Based on the
 20 Bates numbers.
 21 A. No, I am not. I would have to
 22 look at each individual document to refresh
 23 my memory as to what it contains.
 24 ///

1 BY MR. ZELLERS:
 2 Q. Once you looked at these
 3 documents, the Imerys documents and the
 4 documents produced by the Johnson & Johnson
 5 companies, did you ask plaintiffs' counsel
 6 for any additional documents?
 7 A. I did not. My understanding is
 8 that most of these are reports, testing
 9 reports, and most of them are positive
 10 results regarding the presence of asbestos or
 11 fibers in the product. And I know that there
 12 were many others that may not have shown
 13 positive results that I did not look at.
 14 Q. Did you ask the plaintiff
 15 attorneys to show you or provide you with the
 16 testing documentation that showed an absence
 17 of asbestos or asbestos fibers in the talcum
 18 powder?
 19 A. Regarding the test results that
 20 are equivalent to these that were negative,
 21 no, I did not request those.
 22 Q. Did you review documents
 23 relating to any fragrance chemicals that are
 24 contained in or that you believe are

1 contained in the talcum powder?
 2 A. Yes. I did review some lists
 3 and, of course, Dr. Crowley's report.
 4 Q. Do you have any idea or
 5 understanding as to the amount or amounts of
 6 the fragrance chemicals that are contained in
 7 the talcum powder in either the Johnson &
 8 Johnson Consumer company talcum powder that's
 9 involved in this litigation?
 10 MS. O'DELL: Object to the
 11 form.
 12 MR. ZELLERS: Let me withdraw
 13 that.
 14 BY MR. ZELLERS:
 15 Q. Do you know or have any
 16 understanding as to the amounts of fragrance
 17 chemicals that are in the talcum powder?
 18 A. I do not have the specific
 19 formulation or quantities of those substances
 20 that contributed to the products.
 21 Q. Do --
 22 MS. O'DELL: Excuse me.
 23 MR. ZELLERS: Ms. O'Dell,
 24 please, I'm going to let the doctor

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1 finish.

2 MS. O'DELL: In that instance,

3 I don't know that he was, and so if he

4 was, my apologies.

5 MR. ZELLERS: It's okay.

6 MS. O'DELL: I've been on my

7 best behavior today, as you know,

8 so -- but I don't want the witness to

9 feel as if they're being cut off, and

10 because Dr. Carson is a very polite

11 gentlemen, he would let you interrupt

12 him.

13 MR. ZELLERS: Of course.

14 MS. O'DELL: And I don't think

15 that's fair.

16 So, Dr. Carson, if you're

17 finished, great. If you're not, you

18 may continue.

19 A. Well, I was going to say that

20 my opinion is that there are very small

21 quantities of those substances that

22 contribute to the fragrance component.

23 BY MR. ZELLERS:

24 Q. Do you know how those

Page 75

1 quantities of fragrance chemicals may have

2 changed over the years?

3 A. My understanding is they have

4 not changed dramatically, but there have been

5 certain substitutions over time.

6 Q. Do you agree that to the extent

7 that you have reviewed internal documents,

8 either of Imerys or from Johnson & Johnson

9 companies, that you have only reviewed the

10 documents that were hand-selected by the

11 plaintiff lawyers for you to review?

12 MS. O'DELL: Object to the

13 form.

14 A. I agree that the only documents

15 that I've reviewed regarding the internal

16 products of Johnson & Johnson or Imerys are

17 the ones that were provided by the

18 plaintiffs' attorneys.

19 BY MR. ZELLERS:

20 Q. Do you know what percentage of

21 the documents that have been produced in this

22 litigation by the Johnson & Johnson companies

23 and by Imerys you have reviewed?

24 A. Well, based on my general

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1 understanding of business practices and these

2 types of industries, I've reviewed an

3 extremely small percentage of those.

4 Q. Is it your practice in your

5 academic work or your clinical research work

6 to rely on internal company documents?

7 A. Yes, it is.

8 Q. Do you rely on internal company

9 documents when you publish papers?

10 A. In some cases.

11 Q. Can you tell me in what cases

12 or instances you have relied on internal

13 company documents in your publications?

14 A. Well, for example, I did -- I

15 was involved in some research work in

16 conjunction with NIOSH at the O.M. Scott

17 Company at Marysville, Ohio, where we did

18 a -- we performed a research in the company

19 and relied on some internal documents in

20 terms of gauging concentrations, industrial

21 hygiene records and so forth, in order to

22 draw conclusions that were pertinent to those

23 publications.

24 Q. Was that data or were those

Page 77

1 internal communications that you relied on?

2 A. They were both.

3 Q. What is the publication on your

4 CV where you relied on those materials?

5 A. Well, let me see here. I think

6 the first author -- looking back here -- the

7 first author would be Jim Lockey.

8 Q. Looking at page 6?

9 A. It's on page 6, and the --

10 there are two publications there. One is

11 Pulmonary Changes After Exposure to

12 Vermiculite Contaminated With Fibrous

13 Tremolite that appeared in the American

14 Review of Respiratory Disease in 1984.

15 There's another publication

16 which is a book chapter called Pulmonary

17 Hazards From Vermiculite that appeared in a

18 book titled Health Issues Related to Metal

19 and Nonmetallic Mining.

20 Q. Do you agree that when you have

21 been provided only a small subset of the

22 documents of a company relating to a

23 particular product, that those documents can

24 potentially be misleading?

<p style="text-align: right;">Page 78</p> <p>1 MS. O'DELL: Object to the</p> <p>2 form.</p> <p>3 A. I don't agree that that's the</p> <p>4 case because I am capable of understanding</p> <p>5 that it's a subset of available information,</p> <p>6 and I can make a reliable determination on</p> <p>7 the pertinence of that material regardless.</p> <p>8 BY MR. ZELLERS:</p> <p>9 Q. Without looking at any other</p> <p>10 documents or any documents that may put the</p> <p>11 documents you were provided in context?</p> <p>12 MS. O'DELL: Object to the</p> <p>13 form.</p> <p>14 A. It depends on the specific</p> <p>15 case, but I would say in most cases, yes.</p> <p>16 BY MR. ZELLERS:</p> <p>17 Q. In this case, it was not</p> <p>18 necessary for you to look at any documents</p> <p>19 other than those specific documents the</p> <p>20 plaintiffs provided to you; is that your</p> <p>21 testimony?</p> <p>22 MS. O'DELL: Object to the</p> <p>23 form.</p> <p>24 A. Regarding the contribution to</p>	<p style="text-align: right;">Page 80</p> <p>1 department?</p> <p>2 A. She's in my department, yes.</p> <p>3 Q. You understand she's a</p> <p>4 lawyer -- strike that.</p> <p>5 You understand she's an expert</p> <p>6 for the plaintiffs in this litigation?</p> <p>7 A. I didn't know that.</p> <p>8 Q. Dr. Ness never told you that</p> <p>9 she was an expert witness for plaintiffs in</p> <p>10 this matter?</p> <p>11 A. No, we didn't discuss this</p> <p>12 case. We only discussed the issue.</p> <p>13 Q. Any other colleagues that you</p> <p>14 discussed your report and opinions with?</p> <p>15 MS. O'DELL: Object to the</p> <p>16 form.</p> <p>17 A. I think I shared some of my</p> <p>18 thinking with the occupational medicine</p> <p>19 residents as a group and asked them to</p> <p>20 consider certain issues in the case.</p> <p>21 BY MR. ZELLERS:</p> <p>22 Q. Did they contribute to your</p> <p>23 review and analysis and opinions?</p> <p>24 A. We had an interesting</p>
<p style="text-align: right;">Page 79</p> <p>1 my opinions, I would say, yes, it was not</p> <p>2 necessary.</p> <p>3 BY MR. ZELLERS:</p> <p>4 Q. Did you do any independent</p> <p>5 investigation to reach your opinions, other</p> <p>6 than the literature search and review of</p> <p>7 websites that you told us about earlier?</p> <p>8 A. Other than just general</p> <p>9 discussion with colleagues, no.</p> <p>10 Q. Did any of the colleagues that</p> <p>11 you spoke with provide you with any</p> <p>12 substantive support for your opinions?</p> <p>13 A. Not that I can recall. It was</p> <p>14 mostly just helpful feedback.</p> <p>15 Q. The colleagues that you spoke</p> <p>16 with were who?</p> <p>17 A. Various colleagues in my</p> <p>18 department or in the School of Public Health.</p> <p>19 Q. Who?</p> <p>20 A. Well, Dr. George Delclos, who</p> <p>21 is a pulmonologist; Dr. Brett Perkison, who</p> <p>22 is an occupational medicine physician;</p> <p>23 Roberta Ness, who is an epidemiologist.</p> <p>24 Q. Roberta Ness is in your</p>	<p style="text-align: right;">Page 81</p> <p>1 discussion, but I don't think that changed my</p> <p>2 opinions in any way.</p> <p>3 Q. The opinions that you're</p> <p>4 expressing in this case are your opinions; is</p> <p>5 that right?</p> <p>6 A. That's correct.</p> <p>7 Q. Your opinions you set forth in</p> <p>8 your report beginning on page 7; is that</p> <p>9 right?</p> <p>10 A. Let me refer to my report, if</p> <p>11 you don't mind.</p> <p>12 MS. O'DELL: Object to the</p> <p>13 form.</p> <p>14 A. I would say -- I would say in</p> <p>15 answer to that question that, yes, my</p> <p>16 opinions do begin on page 7 of the report.</p> <p>17 BY MR. ZELLERS:</p> <p>18 Q. Your first opinion set forth on</p> <p>19 page 7 is that talcum powder is immunogenic</p> <p>20 and carcinogenic; is that right?</p> <p>21 A. Yes.</p> <p>22 MS. O'DELL: Excuse me.</p> <p>23 BY MR. ZELLERS:</p> <p>24 Q. Your second opinion is that</p>

<p style="text-align: right;">Page 82</p> <p>1 perineal use of talcum powder results in 2 direct exposure to the ovaries either via 3 inhalation or migration through the female 4 reproductive tract, correct? 5 A. I would not phrase the opinion 6 in that way, but in general, that is my 7 opinion, yes. 8 Q. How would you phrase your 9 second opinion? 10 A. I think my second opinion 11 relates mostly to the direct exposure to the 12 reproductive tract that perineal use of 13 talcum powder produces. 14 Q. Are you opining as to 15 inhalation as an exposure of talcum powder to 16 women's ovaries? 17 MS. O'DELL: Object to the 18 form. 19 A. Only as a secondary route of 20 exposure. 21 BY MR. ZELLERS: 22 Q. Is it part of your opinions or 23 do you defer to other experts on inhalation? 24 A. I would include that as my</p>	<p style="text-align: right;">Page 84</p> <p>1 MS. O'DELL: Object to the 2 form. 3 A. It's an anatomical fact. The 4 physiology of the reproductive system does 5 not provide the ovaries with the kind of 6 clearance system that, for example, the lungs 7 would have for inhaled exposures. 8 BY MR. ZELLERS: 9 Q. The words "no intrinsic 10 elimination system," are those your words or 11 are those words that you've seen reported in 12 another study or another paper? 13 A. I think that's a fairly generic 14 description, that those are my words. 15 Q. Your fourth opinion is that you 16 believe that the epidemiological studies on 17 talcum powder and ovarian cancer show about a 18 30% increased risk; is that right? 19 A. Correct. 20 MS. O'DELL: Object to the 21 form. 22 BY MR. ZELLERS: 23 Q. As you told us at the outset, 24 those are all still your opinions, although</p>
<p style="text-align: right;">Page 83</p> <p>1 opinion. 2 Q. So you're testifying here today 3 that the perineal use of talcum powder 4 results in direct exposure to the ovaries 5 through migration through the female 6 reproductive tract and that inhalation also 7 results in exposure of talcum powder to the 8 ovaries; is that right? 9 A. That is correct, but my basic 10 opinion is that perineal use of talcum powder 11 exposes the entire reproductive tract, 12 including the pelvic cavity. So it's a bit 13 more extensive than your phrasing. 14 Q. Your third opinion is very 15 similar to your first opinion, except that 16 here you add that it's your opinion that the 17 ovaries are particularly susceptible to the 18 carcinogenicity of talcum powder because they 19 have, in your words, "no intrinsic 20 elimination system"; is that right? 21 A. That's correct. 22 Q. Is that something you came up 23 with on your own, no intrinsic elimination 24 system?</p>	<p style="text-align: right;">Page 85</p> <p>1 you do believe even stronger that there is a 2 causal association between talcum powder and 3 ovarian cancer; is that right? 4 A. That's correct. 5 Q. Have you published on your 6 theory that baby powder causes ovarian 7 cancer? 8 A. No. 9 Q. Do you have plans to do that? 10 A. Not presently. 11 Q. Have you conducted any tests or 12 experiments to confirm your theory that talc 13 migrates to the ovaries? 14 MS. O'DELL: Object to the 15 form. 16 A. These are conclusions that I 17 have drawn based on published literature. I 18 wouldn't characterize them as a theory. I 19 think they're pretty much established fact. 20 BY MR. ZELLERS: 21 Q. I'm going to ask you about all 22 these opinions, and so we'll go through the 23 literature and determine -- or at least I'll 24 ask you questions about why you think that</p>

<p style="text-align: right;">Page 86</p> <p>1 some of these matters are established fact.</p> <p>2 My question is: Did you do any</p> <p>3 tests or experiments as part of your review</p> <p>4 and analysis in this matter?</p> <p>5 A. I did not.</p> <p>6 Q. Did you do any tests or</p> <p>7 experiments relating to your opinion that</p> <p>8 talc causes cancer via inflammation?</p> <p>9 A. I did not.</p> <p>10 Q. Can you identify any article</p> <p>11 that identifies inflammation anywhere in a</p> <p>12 woman's reproductive tract that results from</p> <p>13 external genital talc application?</p> <p>14 MS. O'DELL: Object to the</p> <p>15 form.</p> <p>16 A. I think there are a number of</p> <p>17 published articles that allude to that</p> <p>18 relationship and draw a fairly strong</p> <p>19 conclusion that it exists.</p> <p>20 MS. O'DELL: Mike, excuse me,</p> <p>21 and I'm sorry to interrupt. We've</p> <p>22 been going over an hour and a half.</p> <p>23 Are you at a point where we can take</p> <p>24 just a short break for...</p>	<p style="text-align: right;">Page 88</p> <p>1 you aware of any article that identifies</p> <p>2 inflammation in a woman's reproductive tract</p> <p>3 resulting from external genital talc</p> <p>4 application?</p> <p>5 MS. O'DELL: Object to the</p> <p>6 form.</p> <p>7 A. I would say that the studies</p> <p>8 which have looked at that have relied on the</p> <p>9 result of internal application to show</p> <p>10 migration. There have been studies that have</p> <p>11 shown inflammation as the result of talc, and</p> <p>12 in my opinion, external application is the</p> <p>13 same as internal application in the</p> <p>14 reproductive tract.</p> <p>15 BY MR. ZELLERS:</p> <p>16 Q. I don't mean to be</p> <p>17 argumentative, and I don't want to be, but</p> <p>18 can you name me an article that identifies</p> <p>19 inflammation in a woman's reproductive tract</p> <p>20 resulting from external genital talc</p> <p>21 application?</p> <p>22 MS. O'DELL: Objection, asked</p> <p>23 and answered.</p> <p>24 A. I can't specifically.</p>
<p style="text-align: right;">Page 87</p> <p>1 MR. ZELLERS: Sure, we can.</p> <p>2 Let me just ask these couple of</p> <p>3 questions, and then we'll take a</p> <p>4 break.</p> <p>5 MS. O'DELL: Sure.</p> <p>6 BY MR. ZELLERS:</p> <p>7 Q. So please identify for me any</p> <p>8 articles that you have reviewed that identify</p> <p>9 inflammation anywhere in a woman's</p> <p>10 reproductive tract resulting from external</p> <p>11 genital talc application.</p> <p>12 MS. O'DELL: Objection to form.</p> <p>13 A. I think -- I think the research</p> <p>14 evidence that includes the epidemiology</p> <p>15 piece, which is limited to external</p> <p>16 application of talcum powder, has significant</p> <p>17 enough correspondence with the biological</p> <p>18 experimentation literature that it allows us</p> <p>19 to draw those conclusions.</p> <p>20 BY MR. ZELLERS:</p> <p>21 Q. I understand you've drawn some</p> <p>22 conclusions here, and I'm going to ask you</p> <p>23 about these conclusions.</p> <p>24 But what my question is: Are</p>	<p style="text-align: right;">Page 89</p> <p>1 MR. ZELLERS: Let's take a</p> <p>2 break.</p> <p>3 THE VIDEOGRAPHER: We're off</p> <p>4 the record, 10:37, end of Tape 1.</p> <p>5 (Recess taken, 10:37 a.m. to</p> <p>6 10:55 a.m.)</p> <p>7 THE VIDEOGRAPHER: We're on the</p> <p>8 record at 10:55, beginning of Tape 2.</p> <p>9 BY MR. ZELLERS:</p> <p>10 Q. Dr. Carson, two of the things</p> <p>11 that you have reviewed since authoring your</p> <p>12 report in November of 2018 that you believe</p> <p>13 support your conclusions in this matter and</p> <p>14 your opinions in this matter are the draft</p> <p>15 screening assessment from Health Canada,</p> <p>16 which we marked as Exhibit 9, and the Taher</p> <p>17 paper, which has been marked as Exhibit 7; is</p> <p>18 that right?</p> <p>19 A. Yes.</p> <p>20 Q. Have you looked into what other</p> <p>21 public health authorities, other than</p> <p>22 Health Canada, have had to say about talc and</p> <p>23 ovarian cancer?</p> <p>24 A. Yes, I have.</p>

1 Q. Did you -- strike that.
 2 Are you familiar with the
 3 Center for Disease Control in the United
 4 States?
 5 A. Yes.
 6 Q. Did you review the CDC and its
 7 position on any relationship between talcum
 8 powder and ovarian cancer?
 9 A. That may have been part of my
 10 review, but I don't specifically recall now
 11 what the CDC has on that issue.
 12 Q. CDC does not list talc or
 13 talcum powder as a risk factor for ovarian
 14 cancer, correct?
 15 A. It's quite possible.
 16 Q. Mayo Clinic and a number of
 17 medical centers do not list talc as a risk
 18 factor for ovarian cancer, correct?
 19 A. That may be true.
 20 Q. Did you consider, or are you
 21 familiar with the National Cancer Institute?
 22 A. I am.
 23 Q. National Cancer Institute is a
 24 leading health authority in the United

1 States; is that right?
 2 A. Yes.
 3 Q. Particularly in the area of
 4 cancer and materials that may or may not be
 5 carcinogenic; is that right?
 6 A. Well, the National Cancer
 7 Institute is responsible for guiding national
 8 research policies as it relates to cancers,
 9 and that's one of their considerations is
 10 substances that may be related to cancer.
 11 Q. When you reviewed what the
 12 National Cancer Institute has determined with
 13 respect to talcum powder and whether or not
 14 it is a risk factor for ovarian cancer, what
 15 did you find?
 16 A. The most recent publication
 17 that I viewed discounts the relationship.
 18 Q. In fact, the National Cancer
 19 Institute has concluded that the weight of
 20 the evidence does not support an association
 21 between perineal talc exposure and increased
 22 risk of ovarian cancer; is that right?
 23 MS. O'DELL: Are you reading a
 24 quote from the document?

1 MR. ZELLERS: I'm asking the
 2 doctor a question.
 3 MS. O'DELL: Okay.
 4 MR. ZELLERS: So --
 5 MS. O'DELL: That's specific
 6 language, and if you have specific
 7 language that you're reading from the
 8 report or you've taken from the
 9 report, I would just ask that you show
 10 the doctor.
 11 MR. ZELLERS: Ms. O'Dell, I
 12 have my question. I'm asking my
 13 question. The doctor can either
 14 answer my question or not answer my
 15 question. I'm not reading from a
 16 document. I'm reading from my notes.
 17 MS. O'DELL: I object to the
 18 form of the question. I think it's
 19 unfair.
 20 MR. ZELLERS: Can you answer
 21 that question, Doctor?
 22 A. I would agree that that
 23 restates the general opinion of the NCI as
 24 published, but in order to verify the

1 specific wording, I would need to look at the
 2 document.
 3 BY MR. ZELLERS:
 4 Q. Why would you rely on
 5 Health Canada but not these other public
 6 health organizations, including Center for
 7 Disease Control and the National Cancer
 8 Institute?
 9 A. Well, there are a number of
 10 reasons. There are lots of public health
 11 organizations. Many of them have different
 12 interests and different approaches in the way
 13 that they address problems. For example,
 14 discussing the National Cancer Institute, its
 15 primary focus is on research and treatments
 16 regarding cancers, not necessarily causes,
 17 but it is a funder of basic research in the
 18 United States.
 19 Health Canada is an
 20 organization whose charge is to -- is to
 21 synthesize public health-related positions
 22 based on evidence and disseminate those to
 23 public -- the public through various
 24 healthcare organizations or agencies. And

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1 for that reason, I think it's important to
2 look at the different focus.

3 Also, the Health Canada report
4 is a more contemporaneous report, which has
5 been based on more recent science than has
6 been considered either by the NCI or some of
7 the other public health organizations.

8 Q. The NCI's most recent update to
9 its publication was January of 2019; is that
10 right?

11 MS. O'DELL: Object to the
12 form.

13 A. It's current in terms of its
14 publication. I don't know that it's January
15 of '19; it may be. But it's still not based
16 on the most recently available literature.

17 BY MR. ZELLERS:

18 Q. But Health Canada is; is that
19 right?

20 A. Health Canada is based on more
21 recent literature than the NCI position.

22 Q. Health Canada and its
23 assessment is based upon the meta-analysis by
24 Taher that we've marked as Exhibit 7; is that

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1 right?

2 A. It is.

3 MS. O'DELL: Object to the
4 form.

5 BY MR. ZELLERS:

6 Q. You have reviewed that paper
7 and you believe it supports and strengthens
8 your opinions in this case; is that right?

9 A. Yes.

10 Q. Does the National Cancer
11 Institute review the peer-reviewed literature
12 as it relates to risk factors for ovarian
13 cancer?

14 A. They have a number of
15 committees that are set up for that purpose,
16 and it is -- it's a committee approach which
17 is handled by a committee chairperson. The
18 National Cancer Institute itself has some
19 oversight of that process, but they defer to
20 the committee chairs.

21 Q. You understand that the Health
22 Canada assessment is a draft; is that right?

23 A. Yes.

24 Q. You understand that it's at the

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1 very beginning of the public comment period,
2 correct?

3 A. Yes.

4 Q. You agree that Health Canada
5 can take up to two years to either take
6 action or no action at all; is that right?

7 A. I don't know that to be the
8 case, but it very well could be.

9 Q. How did you come to learn of
10 the Health Canada risk assessment?

11 A. I believe the attorneys let me
12 know about it.

13 Q. The attorneys for plaintiffs in
14 this matter that retained you?

15 A. Yes.

16 Q. Were you involved in the Health
17 Canada risk assessment prior to its
18 publication?

19 A. No.

20 Q. Have you submitted any comments
21 to Health Canada?

22 A. Not yet.

23 Q. Do you intend to submit
24 comments to Health Canada?

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1 A. I might.

2 Q. What comments do you intend to
3 submit to Health Canada?

4 A. I haven't formulated them yet.

5 Q. Outside of litigation, do you
6 generally rely on draft assessments by
7 regulatory agencies?

8 MS. O'DELL: Object to the
9 form.

10 A. Yes.

11 BY MR. ZELLERS:

12 Q. Are you familiar with the
13 precautionary principle?

14 A. I am.

15 Q. What is the precautionary
16 principle?

17 A. The precautionary principle
18 states that changes should take place in the
19 face of a potential hazard until that hazard
20 is proved not to exist. It's a general
21 precept that's used in the EU, for example,
22 and very different from the one that operates
23 in this country.

24 Q. The principle in this country

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1 is that there needs to be scientific evidence
2 in order to take action; is that right?

3 MS. O'DELL: Object to the
4 form.

5 A. Yes, that's correct.

6 BY MR. ZELLERS:

7 Q. The precautionary principle
8 says even before there's full or complete
9 scientific demonstration of cause and effect,
10 it is appropriate to take a precautionary
11 approach; is that right?

12 A. That's right.

13 Q. The Health Canada follows --
14 strike that.

15 Health Canada follows and has
16 adopted a precautionary approach; is that
17 right?

18 A. Yes.

19 Q. Please review
20 Deposition Exhibit 14.

21 (Carson Deposition Exhibit 14
22 marked.)

23 BY MR. ZELLERS:

24 Q. Deposition Exhibit 14 is the

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1 Health Canada Decision-Making Framework for
2 Identifying, Assessing and Managing Health
3 Risk.

4 Do you see that?

5 A. Yes.

6 Q. If you go to page 5 of
7 Exhibit 14 --

8 MS. O'DELL: Feel free to
9 take -- review the document if you're
10 not familiar with it, Dr. Carson.

11 BY MR. ZELLERS:

12 Q. One of the underlying
13 principles in the Health Canada
14 decision-making framework is use a
15 precautionary approach; is that right?

16 A. That's right.

17 Q. If we go to page 8, Health
18 Canada defines the use of a precautionary
19 approach, and looking at the second sentence:
20 A precautionary approach to decision-making
21 emphasizes the need to take timely and
22 appropriate preventative action, even in the
23 absence of a full scientific demonstration of
24 cause and effect.

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1 Did I read that correctly?

2 A. You did.

3 Q. Is that your understanding of
4 what a precautionary approach is?

5 A. Yes. In general, the
6 precautionary principle can be restated that
7 an ounce of prevention is worth a pound of
8 cure.

9 Q. Health Canada does not require
10 a finding of causation such as required in
11 litigation matters in this country, the
12 United States; is that right?

13 A. In order to adopt a document
14 that has a significant effect on general
15 public health practices, no, it does not.

16 Q. The Taher paper, that's another
17 paper that you have reviewed since you
18 published your report; is that right?

19 A. Which paper? I'm sorry.

20 Q. This is what we've marked as
21 Exhibit 7. You brought it with you here
22 today?

23 A. Okay. Yes.

24 Q. You've read the Taher 2018

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1 manuscript; is that right?

2 A. Yes.

3 Q. Where did you obtain that
4 manuscript from?

5 A. This was obtained directly from
6 one of the coauthors on this study to the
7 plaintiffs' attorneys, who passed it along to
8 me.

9 Q. So one of the coauthors on this
10 study gave it to the plaintiffs' counsel, who
11 then gave it to you; is that right?

12 A. That's correct.

13 Q. Who was the author of this
14 publication, Exhibit 7, that provided the
15 paper to plaintiffs' counsel, if you know?

16 A. I don't recall.

17 Q. But one of these authors; is
18 that right?

19 A. It would -- yes.

20 Q. Why did you not include this
21 paper on either your reliance list or your
22 literature list?

23 A. I didn't have it at the time
24 that those were formulated.

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1 Q. Did you have access to the
2 appendices and supplemental tables that are
3 referred to in the Taher 2018 publication
4 which we've marked as Exhibit 7?
5 A. The ones that are not in
6 this -- in this document or --
7 Q. Yes.
8 A. Those -- I have not thoroughly
9 examined those, but I do have access to them.
10 Q. How do you have access to those
11 appendices and supplemental tables?
12 A. They were also provided to me
13 by plaintiffs' counsel.
14 Q. Has the Taher publication,
15 which we've marked as Exhibit 7, been peer
16 reviewed?
17 A. It's in the process. This is a
18 manuscript that's just been accepted for
19 publication, so it has gone through peer
20 review.
21 Q. It has gone through peer
22 review --
23 A. That's my understanding.
24 Q. -- and Exhibit 7 is the article

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1 that you believe will be published; is that
2 right?
3 A. This is a -- this is a working
4 manuscript which has gone through at least
5 part of the peer-review process. There may
6 be minor edits that occur to this, but this
7 is substantially the final article.
8 Q. How do you know that?
9 A. That's the general process of
10 submitting publications to peer-reviewed
11 article -- journals.
12 Q. How do you know -- I'm sorry,
13 did you finish?
14 A. I'm finished.
15 Q. How did you know the status of
16 the peer-review process with respect to
17 Exhibit 7?
18 A. Because it's been accepted for
19 publication.
20 Q. How do you know that?
21 A. That, I was told by the
22 plaintiffs' attorneys.
23 Q. And you've accepted that; is
24 that right?

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1 A. Yes, I have.
2 Q. Do you know any of the authors
3 of this paper, Exhibit 7?
4 A. No, I don't.
5 Q. Do you know the source of
6 funding for this paper?
7 A. I -- I think the sources of
8 funding are mentioned in here.
9 Q. Other than what's mentioned in
10 the paper, Exhibit 7, do you have any
11 knowledge as to the sources of funding?
12 A. There's a combination of
13 sources. In part, this work is funded
14 through the plaintiffs' attorneys.
15 Q. Have you communicated with any
16 of the authors of this paper?
17 A. No.
18 Q. Do you know the credentials of
19 any of the authors of this paper?
20 A. I haven't investigated that.
21 Q. In your epidemiological work
22 outside of litigation, do you rely on
23 articles that are funded at least in part by
24 plaintiffs' counsel in litigation?

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1 A. If the articles represent good
2 science, I don't really pay much attention or
3 worry about the funding source.
4 Q. Do you know what conflicts of
5 interest any of the authors have?
6 A. I don't know specifically. I
7 can't recall if they're outlined in here.
8 But the -- those are also evaluated based on
9 the peer-review process.
10 Q. Do you know whether some of the
11 authors are serving as consultants to
12 plaintiffs' counsel in this litigation?
13 A. I know that -- no, I don't know
14 that. Excuse me, I gave an incorrect answer.
15 Q. Sure. Correct it, please.
16 A. I mentioned that part of the
17 funding for this research came from
18 plaintiffs' counsel, and I'm not -- I don't
19 know that that's the case. I was thinking of
20 another research report when I said that.
21 Q. Do you know whether or not, at
22 least in part, funding for this paper, the
23 Taher paper, came from plaintiffs' counsel?
24 A. No, I don't.

<p style="text-align: right;">Page 106</p> <p>1 Q. Taher, this paper, Exhibit 7, 2 concludes that asbestos contamination does 3 not explain ovarian cancer, correct? 4 A. It does come to that general 5 conclusion. 6 Q. That's a different conclusion 7 than you have formulated in this matter; is 8 that right? 9 A. No, it's not. 10 Q. You agree that asbestos 11 contamination does not explain ovarian 12 cancer; is that right? 13 A. It doesn't completely explain 14 ovarian cancer. 15 Q. Does it explain ovarian cancer? 16 MS. O'DELL: Objection, asked 17 and answered. 18 A. I -- I don't believe it 19 completely explains ovarian cancer, no. 20 BY MR. ZELLERS: 21 Q. Turn to page 41 of Exhibit 7. 22 Look at the last three lines of the paper. 23 The authors of the Taher publication state: 24 The similarity of findings between studies</p>	<p style="text-align: right;">Page 108</p> <p>1 factors is consistency; is that right? 2 A. Yes. 3 Q. You, in fact, are opining in 4 this case that there is consistency among the 5 talcum powder ovarian cancer studies and 6 publications; is that right? 7 A. Yes. 8 Q. The authors of the Taher paper 9 disagree with that conclusion; is that right? 10 MS. O'DELL: Object to the 11 form. 12 A. I don't think they disagree 13 with that. 14 BY MR. ZELLERS: 15 Q. Turn to page 25, Table 2. This 16 is, again, something that you have reviewed 17 in preparation for your deposition; is that 18 right? 19 A. Well, I didn't review it in 20 preparation for the deposition, but I've 21 reviewed it recently. 22 Q. At the request of plaintiffs' 23 counsel, correct? 24 A. Yes.</p>
<p style="text-align: right;">Page 107</p> <p>1 published prior to and after this point 2 suggest asbestos contamination does not 3 explain the positive association between 4 perineal use of talc powder and the risk of 5 ovarian cancer. 6 Did I correctly state their 7 conclusion? 8 A. Well, there was a final clause 9 of the sentence, but yes, you correctly read 10 that. 11 Q. The Taher authors also 12 discussed the lack of consistency among the 13 various talcum powder studies; is that right? 14 MS. O'DELL: Object to the 15 form. 16 A. I'm sorry, could you repeat 17 that question? 18 BY MR. ZELLERS: 19 Q. Sure. 20 You looked at the Bradford Hill 21 factors in formulating your opinion; is that 22 right? 23 A. Yes. 24 Q. One of the Bradford Hill</p>	<p style="text-align: right;">Page 109</p> <p>1 Q. Table 2 is a summary of 2 evidence for each of the Hill criteria of 3 causation as applied to perineal application 4 of talc and ovarian cancer. 5 Do you see that? 6 A. Yes. 7 Q. Under Consistency, they state 8 that 15 out of 30 studies reported positive 9 and significant associations; is that right? 10 A. Yes. 11 Q. 15 out of 30, that's 50%, 12 right? 13 A. Yes. 14 Q. 50% is no better than a coin 15 toss; is that right? 16 MS. O'DELL: Object to the 17 form. 18 A. Well, I would have to also 19 mention that the majority of those 30 studies 20 found positive associations. These are the 21 ones that showed positive associations that 22 rose to the level of statistical 23 significance. 24 ///</p>

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1 BY MR. ZELLERS:

2 Q. If an association is not
3 statistically significant, then it can be due
4 to chance; is that right?

5 A. But if it's due to chance over
6 and over and over again, and you keep getting
7 a positive association, that argues very
8 strongly against the chance as being the only
9 factor.

10 Q. Can you answer my question: A
11 lack of a statistically significant
12 association is consistent with or can be
13 consistent with no risk, correct?

14 MS. O'DELL: Objection to form,
15 asked and answered.

16 A. If you're referring to an
17 individual study, that might be the case;
18 however, when considering the Bradford Hill
19 criterion of consistency, you look at the
20 overall body of the literature and what it
21 tells you.

22 There's an obvious statistical
23 trend toward positive connection between
24 talcum powder perineal application and the

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1 occurrence of ovarian cancer, and the more
2 evidence that mounts, the more strongly that
3 association is proven.

4 BY MR. ZELLERS:

5 Q. Would you say that 15 out of 30
6 means there are consistent results across
7 studies?

8 A. I think I've just explained to
9 you how I believe there are consistent
10 results across studies.

11 Q. The authors of the Taher paper
12 also conclude that they do not find a
13 consistent dose-response in the papers that
14 look at perineal application of talc and
15 ovarian cancer; is that right?

16 MS. O'DELL: Object to the
17 form.

18 A. Well, what they actually say is
19 that about half of the epidemiological
20 studies assess only one level of talc
21 exposure, ever versus never. So it's not
22 possible from those studies to establish a
23 biological gradient.

24 However, there are a number of

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1 studies that have shown a biological gradient
2 at -- especially in relation to some of the
3 subtypes of ovarian cancer.

4 BY MR. ZELLERS:

5 Q. And I'm going to ask you about
6 those questions, but right now I'm just
7 asking you about the Taher paper.

8 A. Well, I'm trying to just
9 completely answer your question.

10 Q. I'm asking you about the Taher
11 paper. You understand?

12 A. Yes. This is all from the
13 Taher paper that I read you.

14 Q. Section 3.3.1 talks about
15 evidence from human studies. That's on
16 page 20; is that right?

17 A. Yes.

18 Q. This section talks about
19 whether or not there is a consistent
20 dose-response found in those studies; is that
21 right?

22 MS. O'DELL: What sentence are
23 you pointing to?

24 MR. ZELLERS: I'm asking the

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1 doctor questions based upon his review
2 of the paper, Ms. O'Dell.

3 MS. O'DELL: Okay. Feel free
4 to review it, Doctor, if you need to.

5 THE WITNESS: I'm just taking a
6 look at this section.

7 BY MR. ZELLERS:

8 Q. And if it helps you, look on
9 page 21, lines 174 through 177.

10 (Document review.)

11 BY MR. ZELLERS:

12 Q. I only want to ask you about
13 two sentences. Are you ready for me to ask
14 you my question?

15 A. Just one moment, please.

16 Q. Sure.

17 (Document review.)

18 THE WITNESS: All right, I'm
19 ready for your question.

20 BY MR. ZELLERS:

21 Q. The Taher paper states that
22 many of the studies only reported on the
23 ovarian cancer risk assessing one exposure
24 category and that exposure response analyses

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<p>1 were not done in all studies; is that right?</p> <p>2 A. Yes.</p> <p>3 Q. When conducted, findings from</p> <p>4 trend analyses were not consistent; is that</p> <p>5 correct?</p> <p>6 MS. O'DELL: Object to the</p> <p>7 form.</p> <p>8 A. Yes.</p> <p>9 BY MR. ZELLERS:</p> <p>10 Q. All right. With respect -- I'm</p> <p>11 done with that paper.</p> <p>12 You discuss your opinion</p> <p>13 number 1 on page 7 of your report; is that</p> <p>14 right?</p> <p>15 A. Yes.</p> <p>16 Q. You first state on page 7 that</p> <p>17 you believe talcum powder is immunogenic and</p> <p>18 produces chronic inflammation in the tissues;</p> <p>19 is that right?</p> <p>20 A. Yes.</p> <p>21 Q. You state that other components</p> <p>22 in talcum powder, including mineral fibers,</p> <p>23 asbestos, fibrous talc, carcinogenic metals</p> <p>24 and other chemicals intensify the</p>	<p>1 inflammation in the tissues in which it</p> <p>2 sequesters; is that right?</p> <p>3 A. Yes.</p> <p>4 Q. Assuming for the moment that</p> <p>5 talc can reach the ovaries, is it your</p> <p>6 opinion that talc produces chronic</p> <p>7 inflammation in the ovaries and that this</p> <p>8 somehow leads to ovarian cancer?</p> <p>9 A. It is my opinion that talc</p> <p>10 produces chronic inflammation in the</p> <p>11 epithelial tissues of the ovaries and</p> <p>12 surrounding epithelial tissues and leads to</p> <p>13 both carcinogenesis initiation and promotion.</p> <p>14 Q. There are no reports in the</p> <p>15 literature of externally applied talc leading</p> <p>16 to inflammation, granulomas, fibrosis or</p> <p>17 adhesions anywhere along a woman's</p> <p>18 reproductive tract, correct?</p> <p>19 MS. O'DELL: Object to the</p> <p>20 form, asked and answered.</p> <p>21 A. Well, that's similar to the</p> <p>22 question that you asked earlier, and although</p> <p>23 I'm not aware of experimental reports that</p> <p>24 specifically jive with that condition,</p>
Page 115	Page 117
<p>1 inflammatory response and stimulate cell</p> <p>2 growth and proliferation; is that right?</p> <p>3 A. Yes.</p> <p>4 Q. Other than asbestos, what</p> <p>5 mineral fibers in talc intensify the</p> <p>6 inflammatory response?</p> <p>7 A. Well, the endogenous fibrous</p> <p>8 talc fibers also intensify the response.</p> <p>9 Q. Other than asbestos and fibrous</p> <p>10 talc fibers, what mineral fibers in talc do</p> <p>11 you believe intensify the inflammatory</p> <p>12 response?</p> <p>13 A. I'm not really able to answer</p> <p>14 that question because I don't have a specific</p> <p>15 opinion about it. I'm not a geologist.</p> <p>16 Q. Are the other chemicals that</p> <p>17 you refer to in this section fragrance</p> <p>18 chemicals?</p> <p>19 A. Yes.</p> <p>20 Q. Any others?</p> <p>21 A. None that are intentionally</p> <p>22 added.</p> <p>23 Q. You claim, again on page 7,</p> <p>24 that talcum powder produces chronic</p>	<p>1 certainly there are a lot of theoretical</p> <p>2 reports that have been published.</p> <p>3 For example, Dr. Ness' article</p> <p>4 from '99 lays out the theory of inflammation</p> <p>5 and relates that to talc exposure from</p> <p>6 perineal application.</p> <p>7 BY MR. ZELLERS:</p> <p>8 Q. This is your colleague,</p> <p>9 Dr. Ness; is that right?</p> <p>10 A. Ness, and Coussens, when she</p> <p>11 was at Pittsburgh.</p> <p>12 Q. Dr. Ness, you showed her your</p> <p>13 report and asked for her comments; is that</p> <p>14 right?</p> <p>15 A. I didn't show her the report.</p> <p>16 Q. Well, you talked to her about</p> <p>17 and showed her your conclusions and your</p> <p>18 opinions; is that right?</p> <p>19 A. No, I talked to her about the</p> <p>20 paper.</p> <p>21 Q. Her paper?</p> <p>22 A. Yes.</p> <p>23 Q. Did you share with her that you</p> <p>24 were going to be an expert for the plaintiffs</p>

<p style="text-align: right;">Page 118</p> <p>1 in this litigation?</p> <p>2 A. No, I didn't.</p> <p>3 Q. Did she wonder or ask why it</p> <p>4 was that you were researching or looking into</p> <p>5 this issue?</p> <p>6 A. She -- I think she may have,</p> <p>7 yeah.</p> <p>8 Q. And what did you tell her?</p> <p>9 A. I told her I had been recently</p> <p>10 asked to look into it.</p> <p>11 Q. Did you tell her that you'd</p> <p>12 been asked to look into it by counsel for</p> <p>13 plaintiffs in the talc litigation?</p> <p>14 A. No, I didn't.</p> <p>15 Q. And that never came up; is that</p> <p>16 right?</p> <p>17 A. It didn't.</p> <p>18 Q. And she never talked to you or</p> <p>19 told you about her experience and her work as</p> <p>20 counsel -- strike that, as an expert for</p> <p>21 plaintiffs; is that your testimony?</p> <p>22 A. Yes. It was a very brief</p> <p>23 conversation.</p> <p>24 Q. If up to 50% of all U.S. women</p>	<p style="text-align: right;">Page 120</p> <p>1 talc relating to that, and to my knowledge,</p> <p>2 there are no experimental reports or case</p> <p>3 reports that can document that at the current</p> <p>4 time.</p> <p>5 Q. Granulomas, fibrosis and</p> <p>6 adhesions do not cause ovarian cancer,</p> <p>7 correct?</p> <p>8 MS. O'DELL: Object to the</p> <p>9 form.</p> <p>10 A. The inflammatory process that</p> <p>11 is intimately connected with granuloma</p> <p>12 formation may well be the same process that</p> <p>13 results in mutation and promotion of ovarian</p> <p>14 cancer. So I -- I could not agree completely</p> <p>15 with your statement.</p> <p>16 BY MR. ZELLERS:</p> <p>17 Q. Is there a good scientific</p> <p>18 basis today to opine that granulomas,</p> <p>19 fibrosis or adhesions cause ovarian cancer?</p> <p>20 MS. O'DELL: Object to the</p> <p>21 form.</p> <p>22 A. No, I don't think they cause</p> <p>23 ovarian cancer.</p> <p>24 ///</p>
<p style="text-align: right;">Page 119</p> <p>1 have used genital talc, shouldn't there be</p> <p>2 studies which have shown inflammation,</p> <p>3 granulomas, fibrosis or adhesions in a</p> <p>4 woman's reproductive tract?</p> <p>5 MS. O'DELL: Object to the</p> <p>6 form.</p> <p>7 A. Well, there are studies that</p> <p>8 show those things.</p> <p>9 BY MR. ZELLERS:</p> <p>10 Q. Please, tell me the published</p> <p>11 studies that demonstrate inflammation,</p> <p>12 granulomas, fibrosis or adhesions in a</p> <p>13 woman's reproductive tract from externally</p> <p>14 applied talc?</p> <p>15 A. Well, you're adding a new</p> <p>16 condition now.</p> <p>17 Q. I'm sorry if I didn't add that</p> <p>18 before.</p> <p>19 A. There are multiple studies that</p> <p>20 show inflammation and other inflammatory</p> <p>21 reactions in connection with the occurrence</p> <p>22 of ovarian cancer.</p> <p>23 The piece that you're now</p> <p>24 asking for is the external application of</p>	<p style="text-align: right;">Page 121</p> <p>1 BY MR. ZELLERS:</p> <p>2 Q. Would you agree that not all</p> <p>3 inflammatory conditions lead to cancer?</p> <p>4 A. Yes.</p> <p>5 Q. It's true that all of us</p> <p>6 experience inflammatory reactions of one sort</p> <p>7 or another, including chronic conditions,</p> <p>8 that do not lead to cancer, correct?</p> <p>9 A. That's correct. Although there</p> <p>10 is a strong relationship between inflammatory</p> <p>11 processes and the occurrence of cancers, and</p> <p>12 some of those inflammatory diseases that</p> <p>13 you're referring to also have associations</p> <p>14 with increased rates of cancers.</p> <p>15 MR. ZELLERS: Move to strike as</p> <p>16 nonresponsive.</p> <p>17 BY MR. ZELLERS:</p> <p>18 Q. Rheumatoid arthritis is an</p> <p>19 inflammatory condition; is that right?</p> <p>20 A. Yes, it is.</p> <p>21 Q. Does it increase the risk of</p> <p>22 ovarian cancer?</p> <p>23 A. I think I -- it does -- it's</p> <p>24 not associated with ovarian cancer, but I</p>

<p style="text-align: right;">Page 122</p> <p>1 think it may be associated with other 2 cancers.</p> <p>3 Q. Does -- strike that.</p> <p>4 Is psoriasis an inflammatory 5 condition?</p> <p>6 A. Generally, it is.</p> <p>7 Q. Is it associated with an 8 increased risk of ovarian cancer?</p> <p>9 A. Not that I'm aware.</p> <p>10 Q. In your report you state that 11 inflammation is a normal body process that 12 leads to the thwarting of infection and rapid 13 healing; is that right?</p> <p>14 A. That's correct.</p> <p>15 Q. If your inflammation theory is 16 correct, why doesn't inflammation generally, 17 such as in pelvic inflammatory disease, cause 18 ovarian cancer?</p> <p>19 A. It may do so.</p> <p>20 Q. You are opining under oath here 21 that pelvic inflammatory disease causes 22 ovarian cancer?</p> <p>23 A. I think there are experts who 24 have concluded that.</p>	<p style="text-align: right;">Page 124</p> <p>1 A. This is a list that I've put 2 together of some of the studies I've 3 considered and how they relate to things I 4 might testify to today.</p> <p>5 Q. Why did you not tell me about 6 your list that you brought with you today 7 before now?</p> <p>8 A. Well, I'm telling you about it 9 now.</p> <p>10 Q. My question is why did you not, 11 when I asked you what you brought to the 12 deposition today, not take the list out and 13 show us the list?</p> <p>14 A. I didn't think of it.</p> <p>15 Q. Okay. We'll mark your list as 16 Deposition Exhibit 15.</p> <p>17 (Carson Deposition Exhibit 15 18 marked.)</p> <p>19 BY MR. ZELLERS:</p> <p>20 Q. These are a number of notes, 21 four pages of notes. Are these all your 22 notes?</p> <p>23 A. Yes.</p> <p>24 Q. First page has got a section of</p>
<p style="text-align: right;">Page 123</p> <p>1 Q. What study are you relying on 2 for that opinion or statement?</p> <p>3 A. That's not part of the opinions 4 that I've been asked to consider in this -- 5 in this case.</p> <p>6 Q. As you sit here, can you cite 7 me a publication or a study that finds that 8 pelvic inflammatory disease causes ovarian 9 cancer?</p> <p>10 MS. O'DELL: Object to the 11 form.</p> <p>12 A. Well, I have -- I have a list 13 of studies that relate inflammation to 14 ovarian cancer and other cancers.</p> <p>15 BY MR. ZELLERS:</p> <p>16 Q. Can you name me a study or a 17 publication?</p> <p>18 A. Okay. I think I have my list 19 here.</p> <p>20 Q. You brought other materials 21 with you?</p> <p>22 A. I brought this list.</p> <p>23 Q. All right. Well, what list are 24 you pulling out of your pocket?</p>	<p style="text-align: right;">Page 125</p> <p>1 articles on asbestos and ovarian cancer; is 2 that right?</p> <p>3 A. Yes.</p> <p>4 Q. It also has inflammation and 5 cancer and a number of studies; is that 6 right?</p> <p>7 A. Yes.</p> <p>8 Q. Second page has got cohort, 9 where you've listed out the four cohort 10 studies; is that right?</p> <p>11 A. Yes.</p> <p>12 Q. Beneath that are the 13 meta-analyses where you've listed those out 14 and made some notes on those, correct?</p> <p>15 A. Yes.</p> <p>16 Q. The back page of the second 17 page has got a listing of a number of the 18 case-control studies, correct?</p> <p>19 A. Yes. Those are duplicated on 20 another page.</p> <p>21 Q. The third page has got a 22 section on migration and studies that you're 23 looking at for that proposition, correct?</p> <p>24 A. Correct.</p>

<p style="text-align: right;">Page 126</p> <p>1 Q. Underneath that, ovarian cancer 2 risk; is that right?</p> <p>3 A. Yes.</p> <p>4 Q. Underneath that, talc and other 5 cancer; is that right?</p> <p>6 A. Yes.</p> <p>7 Q. And then on the last page, 8 page 4, is a listing of the case-control 9 studies with the odds ratios and confidence 10 intervals; is that right?</p> <p>11 A. For the most part, yes.</p> <p>12 Q. All right. So looking now at 13 your list of studies that you have prepared, 14 which study demonstrates or supports the 15 proposition that pelvic inflammatory disease 16 causes ovarian cancer?</p> <p>17 A. Looking through here, I don't 18 have that item specifically in my notes, but 19 I'm just using my notes to refresh my memory 20 about the individual research report. I 21 think the Coussens and Werb paper from 2010 22 talks about general mechanisms of 23 inflammation in relation to the occurrence of 24 ovarian cancer.</p>	<p style="text-align: right;">Page 128</p> <p>1 authors conclude that pelvic inflammatory 2 disease causes ovarian cancer? Do you 3 believe each of the authors in the studies 4 that you've identified, that their studies 5 stand for that proposition?</p> <p>6 MS. O'DELL: Object to form, 7 asked and answered.</p> <p>8 A. I think all of the studies that 9 I've identified for this question do allude 10 to that, yes.</p> <p>11 BY MR. ZELLERS:</p> <p>12 Q. That pelvic inflammatory 13 disease causes ovarian cancer, correct?</p> <p>14 A. That it is a -- it's a factor, 15 yes.</p> <p>16 Q. It's a cause. That's what they 17 state in those papers, right?</p> <p>18 MS. O'DELL: Object to the 19 form.</p> <p>20 BY MR. ZELLERS:</p> <p>21 Q. That's your testimony?</p> <p>22 MS. O'DELL: Excuse me, 23 misstates his testimony. Object to 24 the form.</p>
<p style="text-align: right;">Page 127</p> <p>1 And there's the Ness and 2 Cottreau paper from '99.</p> <p>3 Okada has discussed it in the 4 2007 paper. And there's a paper from 2001 5 which is Balkwill and Mantovani which 6 discusses the relationship between talc and 7 ovarian cancer and also discusses the 8 relationship to other sources of 9 inflammation.</p> <p>10 Q. Each of those papers that 11 you've identified you believe state that 12 pelvic inflammatory disease is a cause of 13 ovarian cancer, correct?</p> <p>14 MS. O'DELL: Object to the 15 form.</p> <p>16 A. Well, I don't think they state 17 that in so many words, but if you read the 18 paper and you understand that -- what pelvic 19 inflammatory disease is and its relationship 20 to inflammatory processes in general, yes, 21 that's what they're saying.</p> <p>22 BY MR. ZELLERS:</p> <p>23 Q. Doctor, my question to you was: 24 Are you aware of any papers in which the</p>	<p style="text-align: right;">Page 129</p> <p>1 A. I would say it's a factor and 2 leave it at that.</p> <p>3 BY MR. ZELLERS:</p> <p>4 Q. All right. Are you familiar 5 with pleurodesis?</p> <p>6 A. I am.</p> <p>7 Q. Does a pleurodesis cause 8 cancer?</p> <p>9 A. It is not known to, although it 10 might.</p> <p>11 Q. Are you familiar with the 12 study, 1979, A survey of the long-term 13 effects of talc and kaolin pleurodesis?</p> <p>14 A. Can tell me who the author of 15 that was?</p> <p>16 Q. Sure. The author is -- this is 17 from the Research Committee of the British 18 Thoracic Association. The members of the 19 subcommittee were Chappell, Johnson, Charles, 20 Wagner, Seal, Berry and Nicholson.</p> <p>21 Are you familiar with that 22 paper?</p> <p>23 A. I'm not familiar with the 24 paper. I may have looked at it in the past.</p>

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1 Q. We'll take a look at it. We'll
2 mark it as Deposition Exhibit 16.
3 (Carson Deposition Exhibit 16
4 marked.)
5 A. Thank you.
6 MS. O'DELL: Thank you.
7 BY MR. ZELLERS:
8 Q. This was a study that looked at
9 the association between pleurodesis and lung
10 cancer; is that right?
11 A. Yes.
12 Q. It's a study that you cite on
13 page 1 of your literature list; is that
14 right?
15 A. Okay. Yes.
16 Q. So you've read it; is that
17 right?
18 A. I have.
19 Q. You've considered it; is that
20 right?
21 A. Yes.
22 Q. They looked at 210 patients
23 that underwent a pleurodesis with talc or
24 kaolin 14 to 40 years before; is that right?

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1 A. That's correct.
2 Q. And they found that there was
3 no increased incidence of lung cancer and no
4 cases of mesothelioma; is that right?
5 A. That's correct.
6 Q. Why don't -- well, strike that.
7 You're aware of the studies
8 that have looked at antiinflammatory drugs
9 and aspirin use with respect to whether or
10 not they're associated with -- let me
11 withdraw that.
12 Are you familiar with the NSAID
13 and aspirin use studies relating to the
14 incidence of ovarian cancer in chronic users?
15 A. I'm familiar with some of
16 those, yes.
17 Q. If your theory is correct that
18 inflammation causes ovarian cancer, then you
19 would expect that the studies of NSAIDs and
20 aspirin use, antiinflammatory drugs that
21 reduce inflammation, would consistently
22 reduce the incidence of ovarian cancer,
23 correct?
24 MS. O'DELL: Object to the

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1 form.
2 A. I think that was the hypothesis
3 of those research reports.
4 BY MR. ZELLERS:
5 Q. And, in fact, the NSAID studies
6 do not find a consistent causal reduction in
7 the risk of ovarian cancer; is that right?
8 A. I think that's correct.
9 Q. In your report you also state
10 that studies show that use of cornstarch
11 instead of talcum powder reduces the risk of
12 ovarian cancer; is that right?
13 A. Yes.
14 Q. If inflammation causes cancer,
15 why would cornstarch be a superior
16 alternative to talc?
17 A. The reason is that cornstarch,
18 being a biological product, is much -- it
19 does have a rapid clearance from the body,
20 even when sequestered, in comparison with a
21 mineral substance like talc.
22 Q. Well, in fact, cornstarch
23 causes or increases the risk of inflammation,
24 granulomas, fibrosis and adhesions, correct?

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1 A. It may, yes.
2 Q. Just like you claim talcum
3 powder increases the risk of inflammation,
4 granulomas, fibrosis and adhesions; is that
5 right?
6 MS. O'DELL: Object to the
7 form.
8 A. I think you are -- you're
9 parsing terms here. That list of things were
10 your words. I was agreeing with the
11 relationship between talc and inflammation in
12 ovarian epithelial tissue and the production
13 or granulomas. I did not discuss the
14 relationship between talc and adhesions or
15 fibrosis. There was one other thing on your
16 list.
17 BY MR. ZELLERS:
18 Q. Well, in fact, the FDA has
19 banned the use of cornstarch as a powder for
20 lubricating surgical gloves; is that right?
21 A. It has, but that's not the
22 reason.
23 Q. Well, the reason that they
24 banned the use of cornstarch is because it

<p style="text-align: right;">Page 134</p> <p>1 presented an unreasonable and substantial 2 risk of illness or injury and that that risk 3 cannot be corrected or eliminated by 4 labeling, correct? 5 A. I don't know the specific 6 language. It looks like you're reading from 7 a Federal Register document. 8 The main reason that cornstarch 9 has been banned as a lubricant in gloves is 10 because of the potential for transmission of 11 primarily respiratory problems through 12 inhalation, mostly by co-workers, not by 13 patients. 14 Q. You do agree that cornstarch 15 has been banned by the FDA for use in 16 surgical gloves; is that right? 17 A. All powdered gloves have been 18 essentially banned from hospitals and 19 operating rooms now. 20 Q. You also talk about 21 inflammation and oxidative stress; is that 22 right? 23 A. Yes. 24 Q. Does the presence of oxidative</p>	<p style="text-align: right;">Page 136</p> <p>1 Q. Why do you have to have a 2 special definition of "oxidative stress"? 3 I'm asking simply: Is there a publication or 4 a study which documents that oxidative stress 5 is involved in the development of ovarian 6 cancer? 7 MS. O'DELL: Object to the 8 form. 9 A. Sure. 10 BY MR. ZELLERS: 11 Q. And what paper are you going to 12 point me to? 13 A. Well, I'll point you to the 14 Ness paper to begin with, because it was one 15 of the earlier papers that related oxidative 16 stress from talc to the occurrence of ovarian 17 cancer. But the relationship between 18 inflammation, which essentially is the source 19 of the oxidative stress, and cancer goes all 20 the way back into the 19th Century in terms 21 of its proposal as a rationale. 22 Q. Is oxidative stress a variation 23 of inflammation as you're using that term 24 relating to a potential cause of ovarian</p>
<p style="text-align: right;">Page 135</p> <p>1 stress in a tissue indicate that cancer will 2 develop in that tissue? 3 A. No. 4 Q. If exposure to a substance 5 causes oxidative stress in certain tissue, 6 does that mean exposure of all other tissues 7 to that substance will cause oxidative stress 8 in those tissues? 9 A. Not necessarily. 10 Q. Does the body have protective 11 mechanisms that can limit tissue damage from 12 oxidative stress? 13 A. Yes. 14 Q. Do all substances that cause 15 oxidative stress also cause cancer? 16 A. I'm not sure the answer to that 17 question is known. 18 Q. Are there any studies or 19 publications that indicate that oxidative 20 stress is involved in the development of 21 ovarian cancer? 22 A. If I can define the term 23 "oxidative stress," I could give you an 24 answer to that, that question.</p>	<p style="text-align: right;">Page 137</p> <p>1 cancer? 2 A. It's a component of 3 inflammation. 4 Q. As a toxicologist, how would 5 you define fibrous talc? 6 A. Fibrous talc is a form of talc 7 that is conformed into elongated structures 8 that have an aspect ratio of length greater 9 than width that is different from the 10 majority of talc which is the platy form. 11 Q. Do you consider yourself to be 12 an expert on fibrous talc? 13 A. No, I don't. 14 Q. Do you consider yourself to be 15 an expert on oxidative stress? 16 A. I have dealt a lot with issues 17 of oxidative stress and health effects 18 resulting from it. 19 Q. Do you consider yourself to be 20 an expert in oxidative stress? 21 MS. O'DELL: Objection, asked 22 and answered. 23 A. I'm not a specific expert in 24 oxidative stress, but I can -- I can opine</p>

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1 regarding my professional understanding and
2 training.

3 BY MR. ZELLERS:

4 Q. You've never been involved in
5 terms of any research or publication on the
6 subject of oxidative stress and any
7 association with ovarian cancer, correct?

8 A. Not in terms of ovarian cancer,
9 no.

10 Q. You have not been involved in
11 any research or publication relating to the
12 subject of inflammation and its association
13 with ovarian cancer, correct?

14 A. No. All right. Yes, correct.

15 Q. Yes, it is correct? Okay.

16 You claim that the presence of
17 asbestos and fibrous talc further intensifies
18 the carcinogenic effect of talc; is that
19 right?

20 A. Yes.

21 Q. Is that statement different
22 from the statement directly above where you
23 allege that asbestos and mineral fibers
24 intensify the inflammatory response and

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1 stimulate the cell growth and proliferation?

2 A. It's not different, no.

3 Q. Are your opinions dependent on
4 talc containing carcinogenic asbestos and/or
5 fibrous talc?

6 A. No.

7 Q. Do you believe that talcum
8 powder without asbestos causes ovarian
9 cancer?

10 A. I believe talcum powder causes
11 ovarian cancer. I have not seen any research
12 done on talcum powder that has been shown not
13 to contain asbestos.

14 Q. Your assumption that you have
15 made in formulating your opinions here is
16 that talcum powder contains asbestos; is that
17 right?

18 A. No.

19 Q. What assumption have you made
20 as to whether or not talcum powder contains
21 either asbestos or fibrous talc?

22 MS. O'DELL: Object to the
23 form.

24 A. Looking at the research

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1 reports, the epidemiology first, is looking
2 at the relationship between perineal use of
3 dusting powders, talcum powders and ovarian
4 cancer.

5 Although there have been
6 efforts in some of those studies to
7 characterize the proportion or the
8 ingredients that would be either asbestos or
9 fibers, that's not done in all cases, and
10 it's not ruled out in any cases.

11 The -- also, the research
12 studies that have been performed, the
13 testing, for example, of the products
14 themselves are replete with reports of
15 components of these powders that are fibrous
16 in nature.

17 MR. ZELLERS: Move to strike as
18 nonresponsive.

19 BY MR. ZELLERS:

20 Q. Do you believe that all talcum
21 powder products that are on the market
22 contain asbestos?

23 MS. O'DELL: Object to the
24 form.

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1 A. I don't know.

2 BY MR. ZELLERS:

3 Q. Does it matter to your opinion
4 as to whether or not the talcum powder
5 products, and particularly the talcum powder
6 products involved in this case, contain
7 asbestos?

8 A. I wouldn't have a way to be
9 able to answer that yes or no.

10 Q. Do you -- strike that.

11 Have you reached a conclusion
12 as to whether or not the talcum powder
13 products involved in this case contain
14 fibrous talc?

15 A. I think that most of them do.

16 Q. Does all of the talcum powder
17 contain fibrous talc or just some of it?

18 A. Certainly a lot of it does.

19 Q. The basis for your conclusion
20 that the talcum powder at issue in this case
21 contains fibrous talc is the testing reports
22 that plaintiffs' attorneys gave you?

23 MS. O'DELL: Object to the
24 form.

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1 A. Yes. Also Longo's publications
2 and reports.
3 BY MR. ZELLERS:
4 Q. You have reviewed the Longo
5 reports; is that right?
6 A. Yes.
7 Q. Have you ever met with him?
8 A. No.
9 Q. Do you know his qualifications?
10 A. I looked at his qualifications
11 at one point, but I don't recall exactly what
12 it is at this stage.
13 Q. Ever hear of him before this
14 lawsuit, your getting involved in the talc
15 litigation back in October of 2018?
16 A. No.
17 Q. Have you reviewed any of
18 Longo's testing where he did not find
19 asbestos?
20 A. I -- the only thing I've
21 reviewed are what's present in those reports
22 that I cited.
23 Q. Were you provided by counsel
24 for plaintiffs with any testing reports from

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1 Longo where he did not find asbestos?
2 A. There are some of those listed
3 in his reports.
4 Q. Have you reviewed the FDA's
5 testing of talcum powder products?
6 A. The FDA didn't really do much
7 testing of talcum powder products.
8 Q. Have you reviewed the FDA's
9 testing of talcum powder products?
10 MS. O'DELL: Objection, vague.
11 A. The only FDA testing that I
12 looked at was the -- I have it referenced in
13 my list, but the FDA, based on a
14 recommendation, requested samples from
15 various companies, I think nine different
16 sources of talc. They received four and
17 tested those. And based on their test method
18 determined that there was not a -- not
19 evidence of a significant hazard.
20 BY MR. ZELLERS:
21 Q. Have you made any effort to
22 quantify the amount of any alleged
23 contaminant in the Johnson & Johnson Consumer
24 talcum powder?

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1 MS. O'DELL: Object to the
2 form.
3 A. That wasn't my charge. I defer
4 to the other experts in this case.
5 BY MR. ZELLERS:
6 Q. Do you have an opinion on what
7 type of asbestos you believe is in the talcum
8 powder products at issue in this case?
9 A. Well, there have been various
10 types shown, but I think for the most part
11 it's tremolite and anthophyllite.
12 Q. Are you familiar with
13 crocidolite?
14 A. Yes.
15 Q. Is crocidolite found in talcum
16 powder or baby powder?
17 A. It's not commonly found in it.
18 Q. You believe that the
19 asbestos -- types of asbestos that may be in
20 the talcum powder at issue in this case is
21 tremolite and acidolite [sic]?
22 MS. O'DELL: Objection.
23 A. Anthophyllite. There are
24 others found, but you asked for most common.

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1 BY MR. ZELLERS:
2 Q. Most common you believe are
3 tremolite and anthophyllite?
4 A. Anthophyllite.
5 Q. Anthophyllite. Those two; is
6 that right?
7 A. Yes.
8 Q. What types of asbestos are
9 associated with ovarian cancer?
10 A. Well, I'll go back to my list
11 again. Crocidolite is associated with
12 ovarian cancer in the Acheson report from
13 1982, which was from female gas mask
14 manufacturers in England who made gas masks
15 during the period of the Second World War,
16 and crocidolite is associated with that with
17 a fairly high relative risk of 2.96.
18 Chrysotile asbestos had also a positive
19 relative risk of 1.74.
20 There was a study of factory
21 workers and pipe ladders in east London,
22 which is the Berry report from 2000, that
23 showed a relative risk of 2.53, and those
24 workers were exposed to primarily asbestos

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1 cement products and plasters, so the --
2 Q. What type of asbestos, if you
3 know?

4 A. That would have been primarily
5 amphibole asbestos types, which would include
6 crocidolite and tremolite and anthophyllite,
7 amosite is in that category.

8 Bertolotti in 2008 published a
9 report -- actually, there were several
10 reports that resulted from the Eternit
11 factory studies in Casale Monferrato in
12 Italy, which was a plant that manufactured
13 cement sheet and corrugated tubing, and there
14 were a number of studies that showed elevated
15 relative risks in persons exposed to asbestos
16 in that work, and that would also have been
17 amphibole asbestos types.

18 Q. The studies that you've recited
19 for us, those are all occupational studies;
20 is that right?

21 A. Yes. I've got a lot more.

22 Q. Well, and it's on your list,
23 which we marked as Exhibit 15; is that right?

24 A. That's correct.

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1 Q. All right. Those studies did
2 not involve the perineal application of
3 talcum powder products; is that right?

4 MS. O'DELL: Object to the
5 form.

6 A. It was not a factor in the
7 study.

8 BY MR. ZELLERS:

9 Q. Crocidolite and chrysotile
10 asbestos has generally not been found in
11 talcum powder products, correct?

12 A. In general, that's the case.

13 Q. Was there ever a point in time
14 where you believe that the talcum powder
15 products involved in this case were not
16 contaminated with asbestos?

17 MS. O'DELL: Objection to form,
18 vague as to time.

19 A. My understanding is that Imerys
20 and their predecessors and Johnson & Johnson
21 made significant efforts to reduce components
22 of asbestos in their talc products over a
23 number of years and made step-wise progress
24 in doing that.

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1 But based on my current
2 understanding, I don't believe they've ever
3 been totally successful in doing so.

4 So in answer to your question,
5 which I think was, was there ever a point in
6 time where you believe the talcum powder
7 products involved in this case were not
8 contaminated with asbestos, no.

9 BY MR. ZELLERS:

10 Q. You cite in your report,
11 page 5, to two exhibits to the depositions of
12 John Hopkins and Julie Pier in support of
13 your opinion that talcum powder products
14 contain asbestos; is that right?

15 A. That's correct.

16 Q. Looking at page 5, footnote 1,
17 you cite to Exhibit Hopkins-28 in the Hopkins
18 deposition and Exhibit Pier-47 in the Pier
19 deposition; is that right?

20 A. That's correct.

21 Q. Are you aware that those
22 exhibits were created by plaintiffs' counsel?

23 MS. O'DELL: Objection to form.

24 A. I didn't -- I -- I don't know

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1 that and doesn't matter to me.

2 BY MR. ZELLERS:

3 Q. Do you know where the data in
4 those exhibits come from?

5 A. Well, they come from the two
6 persons who are testifying who have produced
7 them from their -- mostly from their business
8 records.

9 Q. Okay. So you believe that
10 Exhibit Hopkins-28 to the Hopkins deposition
11 and Exhibit Pier-47 to the Pier deposition
12 come from the business records of the
13 Johnson & Johnson Company and Imerys?

14 A. From the most part, there was
15 a -- there was a table that was constructed
16 during the deposition which was sort of a
17 piece of summary information. I don't know
18 if it's an exhibit to the deposition or if
19 it's something separate from that, but it
20 would not have been from business records,
21 but occurred at the deposition itself.

22 MS. O'DELL: Excuse me,

23 Dr. Carson, would you like to see a
24 copy of exhibit -- of the Hopkins

<p style="text-align: right;">Page 150</p> <p>1 Exhibit Hopkins-28 and Pier 2 Exhibit Pier-47 in answering these 3 questions? 4 THE WITNESS: If that's easy to 5 do, yes. 6 MS. O'DELL: It's very easy to 7 do. This is a copy of 8 Exhibit Hopkins-28 of the Hopkins 9 deposition and Exhibit Pier-47 of the 10 Pier deposition. 11 THE WITNESS: Okay. 12 BY MR. ZELLERS: 13 Q. Dr. Carson? 14 A. Yes, sir. 15 Q. Did you make any effort to 16 investigate the alternative explanations for 17 the data that's contained in those two 18 exhibits, Exhibit Hopkins-28 and 19 Exhibit Pier-47? 20 A. Alternative explanations, I'm 21 not sure what you mean by that. 22 Q. If the Johnson & Johnson 23 company -- companies' scientists and Imerys' 24 scientists opined that those tests don't</p>	<p style="text-align: right;">Page 152</p> <p>1 exhibits you're looking at, 2 Exhibit Hopkins-28 and Exhibit Pier-47, were 3 included in talcum powder product sold by J&J 4 Consumer Products? 5 MS. O'DELL: Objection to the 6 form, asked and answered. 7 A. No, I don't. 8 BY MR. ZELLERS: 9 Q. Have you confirmed -- strike 10 that. 11 What amount of asbestos 12 exposure is associated with ovarian cancer? 13 A. Any. 14 Q. Your testimony under oath is 15 that any asbestos exposure is associated with 16 ovarian cancer? 17 A. Any asbestos exposure and any 18 perineal application of talcum powder is 19 associated with an increased risk for ovarian 20 cancer. 21 Q. The amount of asbestos 22 contained -- or allegedly contained within 23 the baby powder is of no consequence, 24 correct?</p>
<p style="text-align: right;">Page 151</p> <p>1 actually show asbestos, you have no expertise 2 to dispute that, do you? 3 MS. O'DELL: Object to the 4 form. 5 A. No, I don't have any personal 6 expertise to dispute that. 7 BY MR. ZELLERS: 8 Q. Do you know whether or not any 9 of the talc product that is identified on 10 Exhibit Hopkins-28 and Exhibit Pier-47 was 11 actually used in the talcum powder products 12 that were sold by the Johnson & Johnson 13 Consumer Products company? 14 MS. O'DELL: Objection to form. 15 A. I -- it's my understanding that 16 some of these results, at least -- in 17 particular from the Pier deposition, that 18 some of these results were from testing that 19 was done on material that had already been 20 shipped and probably incorporated into 21 products. 22 BY MR. ZELLERS: 23 Q. Do you know whether or not any 24 of the talc that is referred to on the two</p>	<p style="text-align: right;">Page 153</p> <p>1 MS. O'DELL: Object to the 2 form. 3 A. No, it is of consequence, and a 4 larger dose would be a greater hazard. But 5 that doesn't mean that a low dose is not a 6 hazard. 7 BY MR. ZELLERS: 8 Q. My question is: Do you know 9 the amount of alleged asbestos exposure 10 that's associated with ovarian cancer? 11 A. No. 12 Q. Do you know the type of ovarian 13 cancer that asbestos is associated with? 14 MS. O'DELL: Object to the 15 form. 16 A. It's associated mostly with the 17 collection of epithelial ovarian cancers -- 18 BY MR. ZELLERS: 19 Q. What -- 20 A. -- primarily serous. 21 Q. Does the type of ovarian cancer 22 vary based upon the type of asbestos? 23 A. Not that I'm aware of. 24 Q. You believe that all types of</p>

<p style="text-align: right;">Page 154</p> <p>1 asbestos can produce all types of ovarian 2 cancer; is that correct? 3 MS. O'DELL: Object to the 4 form. 5 A. I suspect that some forms of 6 asbestos are much more carcinogenic than 7 others, and that would be true for the 8 ovaries as well as other structures in the 9 body. 10 BY MR. ZELLERS: 11 Q. Are you able to distinguish for 12 us what types of asbestos cause or are 13 associated with what types of ovarian cancer? 14 A. I don't think I'm able to make 15 those distinctions, but the studies I just 16 read to you regarding the relationship 17 between asbestos and ovarian cancer and the 18 others on my list do indicate that there are, 19 for example, in the Acheson study, there 20 were -- there was a positive relationship 21 between both crocidolite and chrysotile 22 exposure, and the crocidolite had a greater 23 effect on ovarian cancer than the chrysotile, 24 but did not have -- they were both positive.</p>	<p style="text-align: right;">Page 156</p> <p>1 A. That's background information 2 and my personal knowledge. 3 Q. You are not going to give an 4 opinion on mines, mining or milling in this 5 case; is that right? 6 A. Depends on the questions. 7 Q. Well, as you sit here today, do 8 you intend to give opinions on talc mining, 9 mines or milling? 10 A. It wasn't my intention, but if 11 asked a question that I think I'm qualified 12 to answer, I'll try to do it. 13 Q. Are you an expert on talc 14 mining and milling? 15 A. I'm an expert on industrial 16 processes in general, and if -- I have some 17 personal understanding of talc mining and 18 milling. 19 Q. Have you been personally 20 involved in talc mining and milling? 21 A. I haven't been involved in it; 22 I've observed it. 23 Q. Do you consider yourself to be 24 an expert in talc mining and milling?</p>
<p style="text-align: right;">Page 155</p> <p>1 Q. What type of ovarian cancer? 2 A. That, I don't know at the 3 moment. I could look in the paper and see if 4 it's listed. 5 Q. There are a number of different 6 types of ovarian cancer; is that right? 7 A. That's correct. 8 Q. You are not familiar with J&J 9 Consumer Products' procedures for milling or 10 mining; is that right? 11 MS. O'DELL: Object to the 12 form. 13 A. I'm familiar with some of their 14 procedures, yes. 15 BY MR. ZELLERS: 16 Q. Are you familiar with their 17 testing of source mines? 18 A. To some extent. 19 MS. O'DELL: Object to the 20 form. 21 BY MR. ZELLERS: 22 Q. Is it set forth in your report, 23 or is that just background information that 24 you looked at?</p>	<p style="text-align: right;">Page 157</p> <p>1 MS. O'DELL: Objection, asked 2 and answered. 3 A. No, I don't. 4 BY MR. ZELLERS: 5 Q. You have no independent basis 6 to say that cosmetic talc contains asbestos, 7 correct? 8 MS. O'DELL: Object to the 9 form. 10 A. What do you mean by independent 11 basis? 12 BY MR. ZELLERS: 13 Q. You have not done any testing 14 of talcum powder to determine whether it 15 contains asbestos or not; is that right? 16 A. No. All of my understanding is 17 based on other sources. 18 Q. And those other sources would 19 be, in part, the testing that was done by 20 Longo; is that right? 21 A. Yes, as well as the testing 22 that's reported in the -- in the literature 23 section as the Imerys test results and 24 quality control materials.</p>

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1 Q. You're looking now back at the
2 Pier Exhibit Pier-47 and the Hopkins
3 Exhibit Hopkins-28; is that right?

4 A. I was actually referring to the
5 Imerys documents that are referenced toward
6 the end of the literature exhibit to my
7 report, but certainly the Exhibit Pier-47
8 would be included there.

9 Q. You have no independent basis
10 to say that cosmetic talcum powder contains
11 fibrous talc, correct?

12 MS. O'DELL: Object to the
13 form.

14 A. I have no independent basis,
15 no.

16 BY MR. ZELLERS:

17 Q. You're familiar with the
18 limitations of the research on a potential
19 link between asbestos and ovarian cancer; is
20 that right?

21 MS. O'DELL: Object to the
22 form.

23 A. I'm familiar with some research
24 limitations in that question, yes.

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1 BY MR. ZELLERS:

2 Q. You agree that research on the
3 potential relationship between asbestos and
4 ovarian cancer has only considered a small
5 number of cases; is that right?

6 MS. O'DELL: Object to the
7 form.

8 A. Well, it's considered thousands
9 of cases. Certainly in terms of the number
10 of women who have experienced ovarian cancer
11 it's small, but it's significant, and that's
12 where we get research from that answers
13 important questions.

14 BY MR. ZELLERS:

15 Q. Are you familiar with the Reid
16 paper, 2011?

17 A. Yes, but it's been a while
18 since I've looked at it.

19 Q. Well, I'll hand you a copy.
20 We'll mark it as Exhibit 17.

21 (Carson Deposition Exhibit 17
22 marked.)

23 MS. O'DELL: Thank you.

24 ///

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1 BY MR. ZELLERS:

2 Q. The Reid paper that I've handed
3 you, what we've marked as Exhibit 17, looks
4 at the issue: Does exposure to asbestos
5 cause ovarian cancer.

6 Is that right?

7 A. Yes.

8 Q. They talk about in terms of
9 limitations on the first page, right-hand
10 column, they say: Studies that have examined
11 this issue have been limited for two major
12 reasons.

13 Is that right?

14 A. Yes.

15 Q. Number one, small number of
16 cases, much fewer women than men have been
17 exposed to asbestos, particularly in more
18 heavily exposed occupational settings where
19 relative risks are higher; is that right?

20 A. Yes.

21 Q. How many of these studies --
22 well, strike that.

23 Would you agree that the
24 studies in this area have been primarily

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1 related to occupational exposure?

2 A. Primarily, yes.

3 Q. How many total women have been
4 studied?

5 MS. O'DELL: Object to the
6 form. In this study, in this paper,
7 or are you talking about in general?

8 MR. ZELLERS: In general.

9 A. I don't know the answer to
10 that.

11 BY MR. ZELLERS:

12 Q. How many women have been
13 studied in nonoccupational studies?

14 A. Well, very few in comparison to
15 the occupational studies.

16 Q. Are you aware of the
17 difficulties that have existed over time in
18 distinguishing between peritoneal
19 mesothelioma and ovarian cancer?

20 A. Yes.

21 Q. What are those difficulties?

22 A. There is a potential
23 misclassification of one as the other because
24 they have very common habits. They look very

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1 similar under light microscopy, and they're
 2 often difficult to distinguish, even by a
 3 pathologist, unless special tests are used.
 4 Often these cases occur in
 5 places where they don't have the access to
 6 special test equipment that can definitively
 7 distinguish, and so they are classified and
 8 we move on.
 9 Q. Another limitation of any
 10 studies in this area relate to the inability
 11 to account for nonoccupational risk factors
 12 for ovarian cancer other than age; is that
 13 right?
 14 MS. O'DELL: Object to the
 15 form.
 16 A. Are you reading also from this
 17 paper or --
 18 BY MR. ZELLERS:
 19 Q. I was looking now at the
 20 Camargo paper. Are you familiar with the
 21 Camargo paper?
 22 A. If you have a copy of that, I'd
 23 like to look at it, if I'm going to answer
 24 questions about it.

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1 Q. All right. This is a paper in
 2 2011. We'll mark it as Exhibit 18.
 3 (Carson Deposition Exhibit 18
 4 marked.)
 5 BY MR. ZELLERS:
 6 Q. Here the authors also looked at
 7 the issue of occupational exposure to
 8 asbestos and ovarian cancer; is that right?
 9 A. Yes.
 10 Q. If you turn to page 216 -- I'm
 11 sorry, 1216, second-to-last paragraph before
 12 the conclusion: A further limitation of our
 13 analysis was its inability to account for
 14 nonoccupational risk factors for ovarian
 15 cancer other than age.
 16 Is that identified by the
 17 authors as a limitation?
 18 A. Yes, it is.
 19 Q. Under -- if you go a page back,
 20 1215, under Discussion, in the second
 21 paragraph, the authors talk about other
 22 studies that have been done in this area,
 23 including Edelman; is that right?
 24 MS. O'DELL: If you need to

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1 take a minute to refresh yourself on
 2 the page --
 3 MR. ZELLERS: I'm looking under
 4 Discussion.
 5 MS. O'DELL: -- please feel
 6 free to do that.
 7 Excuse me, sir, I was talking.
 8 If you need to review the paper,
 9 Dr. Carson, please feel free to do
 10 that.
 11 MR. ZELLERS: This doctor has
 12 given 35 depositions. He is perfectly
 13 capable of handling himself. He does
 14 not need your advice as we go along.
 15 MS. O'DELL: Nor do I, Michael.
 16 So I'm going to deal with this witness
 17 in the way I choose, which is
 18 perfectly appropriate. If Dr. Carson
 19 needs to review the paper, he's going
 20 to review the paper. You may ask him
 21 questions, he'll be happy to respond.
 22 MR. ZELLERS: Your job is not
 23 to coach the witness; your job is to
 24 make objections as to form or

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1 foundation, not to make speaking
 2 objections and coaching of the
 3 witness.
 4 MS. O'DELL: If you have a
 5 question, I'm sure Dr. Carson would be
 6 happy to address it.
 7 MR. ZELLERS: I've asked him
 8 the question.
 9 MS. O'DELL: Would you mind
 10 repeating the question, please?
 11 MR. ZELLERS: Sure.
 12 THE WITNESS: I don't remember
 13 the question.
 14 MR. ZELLERS: Okay. I'll be
 15 happy to repeat it.
 16 BY MR. ZELLERS:
 17 Q. Dr. Carson, you've looked at
 18 this Camargo paper; is that right?
 19 A. Yes.
 20 Q. In their discussion, they talk
 21 about other research, including research done
 22 by Edelman; is that right?
 23 A. Are you at the top of the
 24 middle column on --

<p style="text-align: right;">Page 166</p> <p>1 Q. I'm looking under Discussion.</p> <p>2 A. Yes.</p> <p>3 Q. The first -- well, the second</p> <p>4 paragraph.</p> <p>5 A. Second paragraph, yes.</p> <p>6 Q. The magnitude of the pooled</p> <p>7 estimate is similar to that reported by</p> <p>8 Edelman; is that right?</p> <p>9 A. Correct. Correct.</p> <p>10 Q. Then they state: They</p> <p>11 concluded, however, that despite the positive</p> <p>12 and significant association, there was</p> <p>13 insufficient information to infer that</p> <p>14 ovarian cancers were caused by occupational</p> <p>15 exposure to asbestos because of concerns</p> <p>16 about tumor misclassification, inappropriate</p> <p>17 comparison populations and the failure to</p> <p>18 take into account for known risk factors.</p> <p>19 Did I read that --</p> <p>20 A. You read that correctly.</p> <p>21 Q. All right. Are women who use</p> <p>22 talc perineally at greater risk of</p> <p>23 mesothelioma?</p> <p>24 A. I can't say that they are, but</p>	<p style="text-align: right;">Page 168</p> <p>1 BY MR. ZELLERS:</p> <p>2 Q. -- if your theory is correct?</p> <p>3 MS. O'DELL: Object to the</p> <p>4 form.</p> <p>5 A. There may have been higher</p> <p>6 rates of ovarian cancers, but you have to</p> <p>7 also understand that the latency period for</p> <p>8 ovarian cancer is pretty long. It's greater</p> <p>9 than 20 years, often as long as 40 years.</p> <p>10 And so we're still dealing with cancers that</p> <p>11 may have started back in the '70s.</p> <p>12 BY MR. ZELLERS:</p> <p>13 Q. Would you agree that exposure</p> <p>14 to asbestos through a perineal cosmetic talc</p> <p>15 use is different from the heavy occupational</p> <p>16 exposure that has primarily been researched?</p> <p>17 MS. O'DELL: Objection to form.</p> <p>18 A. Yes. I agree with that.</p> <p>19 BY MR. ZELLERS:</p> <p>20 Q. Are you an expert and</p> <p>21 knowledgeable about cleavage fragments?</p> <p>22 A. I'm not.</p> <p>23 Q. If I went through a series of</p> <p>24 questions and asked you to differentiate</p>
<p style="text-align: right;">Page 167</p> <p>1 they may be.</p> <p>2 Q. Wouldn't you expect to find</p> <p>3 higher rates of other cancers in women using</p> <p>4 talc like mesothelioma if they are being</p> <p>5 exposed to substantial amounts of asbestos?</p> <p>6 A. Well, we may -- we may be</p> <p>7 seeing some mesotheliomas that are</p> <p>8 misclassified as ovarian cancers, or we may</p> <p>9 be seeing mesotheliomas and not relating talc</p> <p>10 application as a pertinent contributor to</p> <p>11 that case.</p> <p>12 Q. You told us earlier that you</p> <p>13 thought that there may have been more</p> <p>14 asbestos in talcum powders in the 1970s; is</p> <p>15 that right?</p> <p>16 MS. O'DELL: Objection to form.</p> <p>17 A. I think I said there have been</p> <p>18 step-wise improvements, and I -- but I agree</p> <p>19 with that statement.</p> <p>20 BY MR. ZELLERS:</p> <p>21 Q. Shouldn't we have seen higher</p> <p>22 rates of ovarian cancer in the earlier</p> <p>23 studies --</p> <p>24 MS. O'DELL: Object --</p>	<p style="text-align: right;">Page 169</p> <p>1 between cleavage fragments and asbestos</p> <p>2 fibers, you would defer that to other</p> <p>3 experts?</p> <p>4 A. I would.</p> <p>5 Q. You also claim that the</p> <p>6 presence of carcinogenic metals, including</p> <p>7 chromium, cobalt and nickel in talc, adds to</p> <p>8 its carcinogenicity; is that right?</p> <p>9 A. That is right.</p> <p>10 Q. Do you have an opinion or</p> <p>11 knowledge as to the amounts of chromium,</p> <p>12 cobalt and nickel, if any, in talc?</p> <p>13 A. Those metal elements are</p> <p>14 included as -- usually as impurities or in</p> <p>15 very small quantities in some deposits and</p> <p>16 are present in small amounts.</p> <p>17 Q. Do you have any idea how much</p> <p>18 of these metals, if any, reaches a woman's</p> <p>19 ovaries each time they use talc?</p> <p>20 A. I can't tell you how much, but</p> <p>21 I can tell you that some does, and it is --</p> <p>22 it remains in the talc until long after it</p> <p>23 reaches the ovaries.</p> <p>24 Q. Chromium, cobalt and nickel are</p>

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1 natural elements; is that right?
 2 A. Yes.
 3 Q. They are naturally in our
 4 bodies; is that right?
 5 A. That's correct.
 6 Q. They are present in food,
 7 drinking water, bottled water, vitamins; is
 8 that right?
 9 A. To some extent.
 10 Q. Do you have any evidence that
 11 the blood or tissue levels of any trace heavy
 12 metals are higher in genital talc users
 13 compared to nonusers?
 14 MS. O'DELL: Object to the
 15 form.
 16 A. I do not.
 17 BY MR. ZELLERS:
 18 Q. As we discussed when we talked
 19 about asbestos, you cannot evaluate the
 20 potential effects of exposure to a substance
 21 without factoring in the amount of exposure;
 22 is that right?
 23 MS. O'DELL: Object to the
 24 form.

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1 A. It's useful to factor in the
 2 amount if the amount is known. If the amount
 3 is not known, it's not necessarily required
 4 to draw conclusions.
 5 BY MR. ZELLERS:
 6 Q. In this case, you do not know
 7 the amount, be it chromium, cobalt and/or
 8 nickel; is that right?
 9 MS. O'DELL: Objection to the
 10 form.
 11 Excuse me. Dr. Carson, as you
 12 know, is not being offered as a
 13 case-specific expert, so that question
 14 sounds like a specific patient, and so
 15 I would -- that's my objection.
 16 A. I do not know the amount, but
 17 my opinion is that any within the
 18 microenvironment of the inflammatory process
 19 that is occurring due to talc sequestration
 20 is contributing to the carcinogenic
 21 potential.
 22 BY MR. ZELLERS:
 23 Q. But you don't know for any
 24 individual plaintiff their level of exposure

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1 to chromium, cobalt or nickel or any other
 2 heavy metal; is that right?
 3 A. That is correct.
 4 Q. That answer to that question
 5 would be true if I asked you about the
 6 different fragrance chemicals, correct?
 7 MS. O'DELL: Object to the
 8 form.
 9 A. Also true.
 10 BY MR. ZELLERS:
 11 Q. You did a risk assessment in
 12 this matter; is that right?
 13 A. Yes.
 14 Q. Do you agree that a complete
 15 and proper risk assessment involves four
 16 elements?
 17 MS. O'DELL: Object to the
 18 form.
 19 A. Not necessarily.
 20 BY MR. ZELLERS:
 21 Q. Well, you have to identify a
 22 potential hazard; is that right?
 23 A. Yes.
 24 Q. You've got to do some type of

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1 dose-response assessment; is that right?
 2 A. Not necessarily.
 3 Q. You --
 4 MS. O'DELL: Excuse me. If you
 5 finished -- if you need to,
 6 Dr. Carson, if you're not finished.
 7 If you're finished, fine. Sorry.
 8 A. A qualitative risk assessment
 9 does not necessarily require a dose-response
 10 in order to reach valid conclusions.
 11 BY MR. ZELLERS:
 12 Q. It is not necessary to do a
 13 dose-response assessment as part of a risk
 14 assessment. Is that your testimony under
 15 oath?
 16 A. It's not always necessary.
 17 Q. Was it necessary in this case?
 18 A. Well, I think there is an
 19 aspect of dose-response that was performed in
 20 the risk assessment process here.
 21 Q. What dose-response assessment
 22 did you make with respect to chromium, cobalt
 23 and nickel and any other heavy metal?
 24 A. There's no information

<p style="text-align: right;">Page 174</p> <p>1 available to do a dose-response estimate for 2 those metals.</p> <p>3 Q. What information did you rely 4 or use, if any, to make a dose-response 5 assessment with respect to any fragrance 6 chemicals?</p> <p>7 MS. O'DELL: Objection, form.</p> <p>8 A. There is no information 9 available to do a dose-response estimate for 10 the fragrances.</p> <p>11 BY MR. ZELLERS:</p> <p>12 Q. Did you do any type of exposure 13 assessment in this case?</p> <p>14 MS. O'DELL: Object to the 15 form, vague.</p> <p>16 A. I'm not sure exactly what 17 you're -- what you're asking by exposure 18 assessment.</p> <p>19 BY MR. ZELLERS:</p> <p>20 Q. Well, an exposure assessment is 21 also part of a risk assessment; is that 22 right?</p> <p>23 A. In this risk assessment, I 24 considered studies that are reported in the</p>	<p style="text-align: right;">Page 176</p> <p>1 and the metals were there as the baseline 2 component of the talc formation that they 3 came from.</p> <p>4 BY MR. ZELLERS:</p> <p>5 Q. You do not know the amounts of 6 either the heavy metals or the fragrance 7 chemicals in the talcum powder at issue in 8 this case, correct?</p> <p>9 A. That's -- that's correct, I 10 don't.</p> <p>11 Q. You do not know -- well, strike 12 that. I'll withdraw that.</p> <p>13 You brought with you an IARC 14 monograph; is that right?</p> <p>15 A. I have a couple of them.</p> <p>16 Q. All right.</p> <p>17 MS. O'DELL: Are we going to -- 18 are you going to move to --</p> <p>19 MR. ZELLERS: We can take a 20 break if you'd like.</p> <p>21 MS. O'DELL: Yeah, it's been 22 about an hour and a half.</p> <p>23 MR. ZELLERS: Sure.</p> <p>24 THE VIDEOGRAPHER: We're off</p>
<p style="text-align: right;">Page 175</p> <p>1 scientific and medical literature which have 2 reported the assessment of exposure in these 3 cases in various forms, and I considered 4 those exposure assessments as being valid as 5 reported and considered them as a whole.</p> <p>6 Q. Did you look at any exposure 7 assessment specific to the alleged heavy 8 metals contained in talcum powder?</p> <p>9 MS. O'DELL: Object to the 10 form.</p> <p>11 A. No, I did not.</p> <p>12 BY MR. ZELLERS:</p> <p>13 Q. Did you look at any exposure 14 assessment with respect to any fragrance 15 chemicals contained within talcum powder?</p> <p>16 MS. O'DELL: Object to the 17 form.</p> <p>18 A. With respect to the fragrance 19 chemicals and the heavy metals, the only 20 exposure assessment that I was able to do was 21 verify that these things were present in 22 materials.</p> <p>23 The fragrances are always 24 present in whatever form they were added in,</p>	<p style="text-align: right;">Page 177</p> <p>1 the record 12:32, end of Tape 2. 2 (Recess taken, 12:32 p.m. to 3 1:38 p.m.)</p> <p>4 THE VIDEOGRAPHER: We're on the 5 record, 1:38, beginning of Tape 3.</p> <p>6 BY MR. ZELLERS:</p> <p>7 Q. Dr. Carson, when we left, we 8 were talking about the trace metals and 9 fragrance chemicals in talcum powder, 10 correct?</p> <p>11 A. Yes.</p> <p>12 Q. You do not know how much of 13 these trace metals or fragrance chemicals 14 reach the ovaries, correct?</p> <p>15 A. I don't know specifically how 16 much reaches it, but if I know it's a 17 component of the talc, and if I know the talc 18 reaches it, then I know some of the metals 19 and the fragrances reach it.</p> <p>20 Q. You don't know the component or 21 the amount of either the trace metals or the 22 fragrance chemicals in the baby powder, 23 correct?</p> <p>24 A. That's correct.</p>

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1 Q. You do not know the exposure of
2 any of the women who are plaintiffs in this
3 litigation to the talcum powder, correct?

4 MS. O'DELL: Individual women?

5 MR. ZELLERS: Yes, individual
6 women.

7 A. I don't, no.

8 BY MR. ZELLERS:

9 Q. You brought with you an IARC
10 monograph, and I think you've got several
11 monographs that are on your literature list;
12 is that right?

13 A. That's correct.

14 Q. Generally, IARC classifies
15 chemicals and agents from Group 1,
16 carcinogenic to humans, down to Group 4,
17 probably not carcinogenic to humans; is that
18 right?

19 A. That's correct.

20 Q. Does the classification of a
21 substance as a known probable or possible
22 carcinogen by IARC, and IARC is International
23 Agency for Research on Cancer, or by the
24 National Toxicology Program or the U.S.

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1 Environmental Protection Agency, mean that
2 the substance can cause all types of cancers
3 in humans by any exposure route?

4 MS. O'DELL: Object to the
5 form.

6 A. No.

7 BY MR. ZELLERS:

8 Q. There are different cancers
9 that may be associated with different
10 chemicals or agents; is that right?

11 A. And different routes of
12 exposure.

13 Q. You can have an agent that is a
14 carcinogen or a probable or possible
15 carcinogen for one type of cancer, but not
16 for another type of cancer, correct?

17 A. That's correct.

18 Q. You can have an agent or a
19 chemical that's a carcinogen for one route of
20 exposure for a chemical or agent but is not
21 carcinogenic for a different route of
22 exposure, correct?

23 MS. O'DELL: Objection to form.

24 A. Yes.

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1 BY MR. ZELLERS:

2 Q. What -- would you agree that,
3 in general, metals can differ in their
4 toxicity and potential carcinogenicity based
5 on their form?

6 A. Yes.

7 Q. Do you know the forms of
8 chromium, nickel and cobalt detected in
9 cosmetic talc?

10 A. There's -- metal ions are
11 usually incorporated in the mineral lattice,
12 and so they are part of the magnesium
13 silicate crystal.

14 Q. I'm not sure if that answers my
15 question, and if it does, I don't understand,
16 so let me ask again.

17 Do you know the forms, and by
18 that I mean valence state, of chromium or
19 nickel or cobalt that have been detected in
20 cosmetic talc?

21 A. Oh, the valence state?

22 Q. Yes, sir.

23 A. I don't know specifically, but
24 that's dependent on the surrounding structure

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1 that the metals are contained in, and metals
2 can assume a different valence state
3 depending on the redox environment.

4 Q. You are not, at least in this
5 litigation today, expressing any opinion as
6 to the valence state of chromium that may be
7 found in cosmetic talc, correct?

8 MS. O'DELL: Object to the
9 form.

10 A. No, I'm not.

11 BY MR. ZELLERS:

12 Q. Your second opinion is that the
13 perineal use of talcum powder results in
14 direct exposure to the ovaries either via
15 inhalation or migration through the female
16 reproductive tract; is that right?

17 A. Well, it's primarily through
18 the female reproductive tract. The
19 inhalation exposure would be a secondary
20 route.

21 Q. Let me ask you a couple of
22 questions about inhalation exposure.

23 You do not cite any studies in
24 the body of your report evidencing that

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1 talcum powder can reach the ovaries through
2 inhalation, correct?

3 MS. O'DELL: Object to the
4 form.

5 A. That is correct, although
6 there -- yes, that's correct.

7 BY MR. ZELLERS:

8 Q. You have never performed any
9 study yourself pertaining to whether inhaled
10 talc can migrate to the ovaries; is that
11 right?

12 A. I have not, although it has
13 been used as an explanation of how talc
14 particles might have reached the ovaries in
15 persons who did not have another form of
16 exposure.

17 Q. If inhalation is the exposure
18 path for talc, shouldn't the lungs bear more
19 of a burden?

20 A. Yes.

21 Q. Why, then, isn't there an
22 epidemic of mesothelioma in women who use
23 talcum powder?

24 A. Because the primary route is

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1 perineal via the reproductive tract.

2 Q. You discuss that on page 7 of
3 your report; is that right?

4 A. Yes.

5 Q. You cite a number of studies
6 for the proposition that talc can be
7 transported from the perineum to the upper
8 reproductive tract and body cavity; is that
9 right?

10 A. That's correct.

11 Q. None of the articles that you
12 cite actually looked at whether talc can
13 migrate from perineal application through the
14 fallopian tubes to the ovaries, did they?

15 A. Let me just refresh my memory
16 for a moment here. Egli was carbon black.
17 Venter was radioactive technetium labeled
18 albumin. Let me see. Blumenkrantz -- I have
19 my notes here.

20 Yeah, I can't remember what the
21 substance was in Blumenkrantz. Sjösten,
22 starch -- yeah, Blumenkrantz was retrograde
23 menstruation. Halme was talc.

24 Q. Which study was talc?

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1 A. The -- I'm sorry. The Heller
2 study was talc, which I didn't cite here.
3 Halme was a retrograde menstruation study via
4 the fallopian tubes, and Sjösten was starch
5 particles.

6 Q. The only study -- and this is
7 not one that you cited, but you've now
8 referred to that involved talc, was Heller;
9 is that right?

10 A. Well, it looked at -- it didn't
11 look at transport inasmuch as it looked at
12 the presence of talc particles in the ovaries
13 and found them with or without the history of
14 talc powder use.

15 Q. Heller looked at 24 patients;
16 is that right?

17 A. I don't know, but that sounds
18 about right.

19 Q. Half of them had a history of
20 using talc products, half did not?

21 MS. O'DELL: Object to form.

22 A. That's correct.

23 BY MR. ZELLERS:

24 Q. Heller found talc in the

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1 tissues of all 24 patients; is that right?

2 A. That is correct.

3 Q. I believe we covered this
4 before, but just to confirm: There are no
5 published articles that you're aware of that
6 show granulomas, fibrosis or adhesions
7 anywhere in the reproductive tract of a woman
8 as a result of external genital talc
9 application, correct?

10 MS. O'DELL: Object to the
11 form.

12 A. I believe that's the case,
13 although there have been granulomas found in
14 some cases of cancer where they reported
15 having used talc.

16 BY MR. ZELLERS:

17 Q. Of the cases or the studies you
18 cited here, Egli, that involved just three
19 women, correct?

20 A. That was just -- that was an
21 experimental study of the transport of carbon
22 particles.

23 Q. The women were in a lithotomy
24 position; is that right?

<p style="text-align: right;">Page 186</p> <p>1 A. That's correct.</p> <p>2 Q. And that means that they had</p> <p>3 their legs up in the air, correct?</p> <p>4 A. Correct.</p> <p>5 Q. Those conditions -- well,</p> <p>6 strike that.</p> <p>7 They were injected with</p> <p>8 oxytocin; is that right?</p> <p>9 A. It is.</p> <p>10 Q. That was to aid in the</p> <p>11 transport of the particles, correct?</p> <p>12 MS. O'DELL: Object to the</p> <p>13 form.</p> <p>14 A. I believe that was the author's</p> <p>15 theory.</p> <p>16 BY MR. ZELLERS:</p> <p>17 Q. Those are different</p> <p>18 circumstances or conditions from a woman who</p> <p>19 would apply a talc to her genital area</p> <p>20 standing up, correct?</p> <p>21 A. Well, they are, but I'm not</p> <p>22 sure that that position is really pertinent</p> <p>23 to the migration of particles through the</p> <p>24 reproductive tract.</p>	<p style="text-align: right;">Page 188</p> <p>1 of all these studies -- that they were using</p> <p>2 various particles that could be detected at</p> <p>3 the other end, and so this was an attempt to</p> <p>4 do an experimental study which would cause no</p> <p>5 harm that would give them an answer regarding</p> <p>6 transport through the reproductive tract.</p> <p>7 Q. In this study, particles were</p> <p>8 introduced into the reproductive tract, not</p> <p>9 externally; is that right?</p> <p>10 MS. O'DELL: Object to the</p> <p>11 form.</p> <p>12 A. That is correct.</p> <p>13 BY MR. ZELLERS:</p> <p>14 Q. Women were given Pitocin to</p> <p>15 stimulate uterine contractions; is that</p> <p>16 right?</p> <p>17 A. That's the same as oxytocin.</p> <p>18 Q. And that's a yes, correct?</p> <p>19 A. Yes.</p> <p>20 Q. Again, as with the Egli study,</p> <p>21 the women were inverted in the Trendelenburg</p> <p>22 position with their head down, legs up when</p> <p>23 the particles were administered; is that</p> <p>24 right?</p>
<p style="text-align: right;">Page 187</p> <p>1 Q. Is it your pos- -- is it your</p> <p>2 testimony that if a woman is in a lithotomy</p> <p>3 position with their legs up into the air,</p> <p>4 that that is comparable with respect to the</p> <p>5 migration of talc to a woman who's standing</p> <p>6 up and using it in her perineal region?</p> <p>7 A. It may be.</p> <p>8 Q. Are you an expert on that?</p> <p>9 A. I'm not.</p> <p>10 Q. The authors in Egli, they</p> <p>11 stated it was possible that the study</p> <p>12 observed false positives due to sample</p> <p>13 contamination because they failed to use</p> <p>14 liquid or filter blanks as negative controls,</p> <p>15 correct?</p> <p>16 A. I don't recall that, but that</p> <p>17 may be the case.</p> <p>18 Q. You refer to a study by Venter.</p> <p>19 That involved a radioactive particulate</p> <p>20 matter, correct?</p> <p>21 A. Yes.</p> <p>22 Q. Did not involve talc particles,</p> <p>23 correct?</p> <p>24 A. The point of the study was --</p>	<p style="text-align: right;">Page 189</p> <p>1 A. I believe so.</p> <p>2 Q. Is it possible that the</p> <p>3 radionuclides can leach from the particles?</p> <p>4 A. I don't know the answer to</p> <p>5 that, but it was radioactive technetium that</p> <p>6 was bound to albumin.</p> <p>7 Q. The Sjösten study that you</p> <p>8 cite, that did not use -- involve the</p> <p>9 perineal use of talc, but an exam with a</p> <p>10 force to the cervix; is that right?</p> <p>11 A. Excuse me. An exam with what?</p> <p>12 Q. So it involved an exam with</p> <p>13 force to the cervix?</p> <p>14 MS. O'DELL: Object to the</p> <p>15 form.</p> <p>16 A. Well, this was -- this was done</p> <p>17 as an experimental study on women who were</p> <p>18 scheduled to get hysterectomies and they did</p> <p>19 it on some women one day prior to the</p> <p>20 hysterectomy and another group of women four</p> <p>21 days prior to the hysterectomy, and they used</p> <p>22 gloves that were powdered with starch and</p> <p>23 gloves that were not powdered with starch.</p> <p>24 And so they had what's called a</p>

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1 Latin square design, and they were able at
2 the point of the hysterectomy of taking
3 samples of the fallopian tubes and washing
4 them to determine whether or not particles
5 were found in the tubes.

6 BY MR. ZELLERS:

7 Q. What they actually found was
8 that, whether the women were examined with
9 gloves with the starch particles or not, they
10 found starch particles in both, both groups,
11 correct?

12 A. It is true.

13 Q. Tubal ligation, you refer to
14 tubal ligation and use that or purport to say
15 that that supports your migration theory,
16 correct?

17 A. It does.

18 Q. Your testimony is that for
19 patients who have had a tubal ligation, that
20 they are at a lesser risk of the talc -- let
21 me withdraw that.

22 Explain to us very briefly why
23 you believe that tubal ligation supports your
24 migration theory.

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1 A. If the pathway of exposure of
2 the ovaries that results in ovarian cancer is
3 via the reproductive tract, then tubal
4 ligation, which closes off the fallopian
5 tubes, would interrupt that pathway and
6 result in reduced exposure; therefore, you
7 would expect a reduced incidence of cancer in
8 those women.

9 Q. In fact, though, that is not
10 what has been reported or at least that has
11 not been consistently reported in the
12 studies; is that right?

13 A. Well, it actually has been a
14 positive factor in a number of the
15 epidemiologic studies that have looked at the
16 ovarian cancer incidence and have been able
17 to include tubal ligation as a historical
18 factor in their analysis.

19 Q. Did you look at the Terry 2013
20 meta-analysis?

21 A. Yes.

22 Q. You cite that in support of
23 your positions in this case; is that right?

24 A. I did.

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1 Q. In fact, in Terry -- well, and
2 let me mark it for you so you've got it in
3 front of you.

4 THE WITNESS: Okay. I'm going
5 to move this binder for the time
6 being, if you don't mind.

7 MR. ZELLERS: Oh, yes, I'll
8 hand you the articles that I refer to,
9 but if you need it, just pull it out.

10 THE WITNESS: Thank you.
11 (Carson Deposition Exhibit 19
12 marked.)

13 BY MR. ZELLERS:

14 Q. Deposition Exhibit 19 is the
15 2013 Terry meta-analysis that you referred to
16 in your report; is that right?

17 A. Yes.

18 Q. That's a pooled analysis of
19 eight studies; is that right?

20 A. Yes.

21 Q. Okay. This pooled analysis of
22 eight studies relating to genital powder use
23 and the risk of ovarian cancer shows no
24 variation in the risk in talc users based on

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1 whether they had a tubal ligation or
2 hysterectomy; is that right?

3 A. I think that's the conclusion
4 of the authors here, but it's not the
5 conclusion of the individual authors of the
6 studies who did the original investigations.

7 Q. Well, it is the conclusion of
8 the authors based upon their meta-analysis of
9 eight studies; is that right?

10 MS. O'DELL: Object to the
11 form.

12 A. Let me just check that.
13 (Document review.)

14 A. Yes.

15 BY MR. ZELLERS:

16 Q. If you look at pages 819,
17 carried over to 820, I'm reading: Our
18 finding of slightly attenuated associations
19 following exclusion of women with powder
20 exposure after tubal ligation or hysterectomy
21 are not supportive of this hypothesis, but
22 risk estimates in this subgroup analysis may
23 have randomly differed from those including
24 all women because of the reduction in sample

<p style="text-align: right;">Page 194</p> <p>1 size.</p> <p>2 Is that right?</p> <p>3 A. Yes.</p> <p>4 Q. Essentially, looking at these</p> <p>5 eight studies in this meta-analysis, Terry</p> <p>6 did not find that exposure to genital powder</p> <p>7 applications that occurred before tubal</p> <p>8 ligation or hysterectomy made any substantive</p> <p>9 difference in the results; is that right?</p> <p>10 A. Yes, but the point is that the</p> <p>11 authors didn't find that it did not make a</p> <p>12 difference either. They -- they ended up</p> <p>13 with a study with reduced numbers that they</p> <p>14 couldn't make determinations about.</p> <p>15 Q. If, though, the migration</p> <p>16 theory is correct, you would expect that</p> <p>17 there would be a reduction in the incidence</p> <p>18 of ovarian cancer for women who have had a</p> <p>19 tubal ligation or hysterectomy; is that</p> <p>20 right?</p> <p>21 MS. O'DELL: Object to the</p> <p>22 form.</p> <p>23 A. Yes, that is correct.</p> <p>24 ///</p>	<p style="text-align: right;">Page 196</p> <p>1 THE WITNESS: Thank you.</p> <p>2 MS. O'DELL: Thank you.</p> <p>3 BY MR. ZELLERS:</p> <p>4 Q. This is also a study,</p> <p>5 Exhibit 20, Cramer 2016, that you cite as</p> <p>6 supportive of your opinions in this case,</p> <p>7 correct?</p> <p>8 A. Correct.</p> <p>9 Q. Cramer actually looked at</p> <p>10 whether or not there was any greater</p> <p>11 association of talc use and ovarian cancer</p> <p>12 and whether or not women who had a tubal</p> <p>13 ligation or hysterectomy had a reduced</p> <p>14 incidence of the disease; is that correct?</p> <p>15 A. Yes.</p> <p>16 Q. Turn to page 337, and then it</p> <p>17 carries over to 339. They're talking --</p> <p>18 they, being the authors -- of their results,</p> <p>19 and I'm reading just at the very bottom of</p> <p>20 337, carried over to 339: By test for</p> <p>21 interaction, column 3, the association was</p> <p>22 significantly greater for women who were</p> <p>23 African-American, had no personal history of</p> <p>24 breast cancer, had a tubal ligation or</p>
<p style="text-align: right;">Page 195</p> <p>1 BY MR. ZELLERS:</p> <p>2 Q. And that was not found in the</p> <p>3 Terry meta-analysis that you cite; is that</p> <p>4 right?</p> <p>5 MS. O'DELL: Object to the</p> <p>6 form.</p> <p>7 A. That is correct, but it was</p> <p>8 found in the baseline studies that were, in</p> <p>9 part, included in this meta-analysis.</p> <p>10 BY MR. ZELLERS:</p> <p>11 Q. Are you -- you also cite the</p> <p>12 Cramer study, 2016; is that right?</p> <p>13 A. Yes.</p> <p>14 Q. I've got a few questions for</p> <p>15 you on the Cramer study, but let me just ask,</p> <p>16 since we're at this part right now.</p> <p>17 Do you have the Cramer study?</p> <p>18 I'll hand it to you.</p> <p>19 A. If you have a copy, I'd</p> <p>20 appreciate it.</p> <p>21 MR. ZELLERS: Sure. We'll mark</p> <p>22 the Cramer study as Exhibit 20.</p> <p>23 (Carson Deposition Exhibit 20</p> <p>24 marked.)</p>	<p style="text-align: right;">Page 197</p> <p>1 hysterectomy.</p> <p>2 Is that right?</p> <p>3 MS. O'DELL: Object to the</p> <p>4 form.</p> <p>5 A. Beginning on page 337?</p> <p>6 BY MR. ZELLERS:</p> <p>7 Q. Yes.</p> <p>8 A. I'm sorry, if you could --</p> <p>9 Q. Sure. At the very end of 337.</p> <p>10 A. Okay.</p> <p>11 Q. So they're looking at --</p> <p>12 A. Oh, by tests for interaction.</p> <p>13 Q. Yes.</p> <p>14 A. Yeah.</p> <p>15 Q. So if your migration theory is</p> <p>16 correct, you would expect there to be a lower</p> <p>17 incidence of ovarian cancer in women who have</p> <p>18 had a tubal ligation or hysterectomy,</p> <p>19 correct?</p> <p>20 MS. O'DELL: Object to the</p> <p>21 form.</p> <p>22 A. That is correct.</p> <p>23 BY MR. ZELLERS:</p> <p>24 Q. All right. Cramer finds by</p>

<p style="text-align: right;">Page 198</p> <p>1 test for interaction the association was</p> <p>2 significantly greater for women who -- and</p> <p>3 then I'm skipping African-American, but I'm</p> <p>4 coming down to -- have a tubal ligation or</p> <p>5 hysterectomy.</p> <p>6 Is that correct?</p> <p>7 A. Yes.</p> <p>8 Q. All right. If talcum powder</p> <p>9 migrates from the perineal region to the</p> <p>10 ovaries, shouldn't exposure to -- exposure to</p> <p>11 talc be far greater in concentration in the</p> <p>12 rectal, vulvar, vaginal, cervical and uterine</p> <p>13 tissues which are closer to the area of</p> <p>14 initial exposure?</p> <p>15 MS. O'DELL: Objection to form.</p> <p>16 A. Well, the acute exposure would</p> <p>17 be greater.</p> <p>18 BY MR. ZELLERS:</p> <p>19 Q. You would expect because the</p> <p>20 acute exposure is greater, that there should</p> <p>21 be inflammation caused in these organs and</p> <p>22 areas, correct?</p> <p>23 A. No. The inflammation and</p> <p>24 oxidative stress is an ongoing process that</p>	<p style="text-align: right;">Page 200</p> <p>1 to talcum powder?</p> <p>2 MS. O'DELL: Object to the</p> <p>3 form.</p> <p>4 A. It doesn't -- it doesn't</p> <p>5 eliminate exposure, but it does remove</p> <p>6 residual exposure, as does sweating, other</p> <p>7 body secretions and so forth.</p> <p>8 BY MR. ZELLERS:</p> <p>9 Q. Are you aware of any studies</p> <p>10 that show inflammation or oxidative stress as</p> <p>11 a result of genital talc use in the rectal,</p> <p>12 vulvar, vaginal, cervical and uterine</p> <p>13 tissues?</p> <p>14 A. No, I'm not.</p> <p>15 Q. Under your theory or belief</p> <p>16 that talcum powder travels from the perineal</p> <p>17 region to the ovaries through the woman's</p> <p>18 reproductive tract, talcum powder must travel</p> <p>19 past the labia, through the vagina, through</p> <p>20 the cervix, and then to the uterus; is that</p> <p>21 right?</p> <p>22 A. That's correct.</p> <p>23 Q. And then the powder travels</p> <p>24 through the uterus and into the fallopian</p>
<p style="text-align: right;">Page 199</p> <p>1 has to develop over time, and it occurs on a</p> <p>2 chronic basis in areas where foreign bodies</p> <p>3 locate and reside. And talc and talcum</p> <p>4 powder are examples of foreign bodies that</p> <p>5 have the right characteristics to cause</p> <p>6 chemotaxis in reactive oxygen species and</p> <p>7 oxidative status.</p> <p>8 Q. Well, in fact, there would be</p> <p>9 chronic exposure, so if we're dealing with,</p> <p>10 as you described in the very beginning, which</p> <p>11 you were asked, to look at the habitual use</p> <p>12 of talcum powder, that would create exposure</p> <p>13 on a chronic basis to the rectal area and</p> <p>14 tissues, vulvar, vaginal, cervical and</p> <p>15 uterine tissues; is that right?</p> <p>16 MS. O'DELL: Object to the</p> <p>17 form.</p> <p>18 A. I suspect if one doesn't bathe,</p> <p>19 that would be more of an issue, but most</p> <p>20 people bathe regularly as well.</p> <p>21 BY MR. ZELLERS:</p> <p>22 Q. And bathing regularly</p> <p>23 eliminates any exposure in the rectal,</p> <p>24 vulvar, vaginal, cervical and uterine tissues</p>	<p style="text-align: right;">Page 201</p> <p>1 tubes to reach the ovaries; is that right?</p> <p>2 A. Yes.</p> <p>3 Q. On what studies are you relying</p> <p>4 to say that talcum powder affects the body</p> <p>5 differently when it's applied to the perineal</p> <p>6 region and travels to the cervix compared to</p> <p>7 when it is applied directly to the cervix?</p> <p>8 A. I don't think --</p> <p>9 MS. O'DELL: Object to the</p> <p>10 form.</p> <p>11 A. -- there is much of a</p> <p>12 difference.</p> <p>13 BY MR. ZELLERS:</p> <p>14 Q. You would expect there to be a</p> <p>15 comparable similar result whether talcum</p> <p>16 powder is applied directly to the cervix</p> <p>17 through the use of dusting of a diaphragm as</p> <p>18 there is to the use of talcum powder in the</p> <p>19 genital areas; is that right?</p> <p>20 A. That is correct. I think the</p> <p>21 two differ probably in terms of quantity very</p> <p>22 significantly. But other than that, they</p> <p>23 would be the same.</p> <p>24 Q. When applied to the perineal</p>

<p style="text-align: right;">Page 202</p> <p>1 region, talcum powder would also be in close</p> <p>2 contact with a woman's urethra; is that</p> <p>3 right?</p> <p>4 A. Yes.</p> <p>5 Q. Substances, and in your view,</p> <p>6 talcum powder, are capable of traveling up</p> <p>7 the urethra; is that right?</p> <p>8 MS. O'DELL: Object to the</p> <p>9 form.</p> <p>10 A. The urethra has a sphincter</p> <p>11 which prevents transport beyond that point.</p> <p>12 BY MR. ZELLERS:</p> <p>13 Q. Women get urinary tract</p> <p>14 infections when bacteria travels up the</p> <p>15 urethra; is that right?</p> <p>16 A. That's correct.</p> <p>17 Q. Studies, though, do not show an</p> <p>18 increase in bladder cancer with talcum powder</p> <p>19 use; is that right?</p> <p>20 A. I don't believe that talcum</p> <p>21 powder transports in any appreciable amount</p> <p>22 up the urethra into the bladder.</p> <p>23 Q. Studies do not show an increase</p> <p>24 in rectal cancer with talcum powder use, do</p>	<p style="text-align: right;">Page 204</p> <p>1 about to reconsider that?</p> <p>2 A. Because the chatter is that</p> <p>3 this is something that's on their radar</p> <p>4 screen currently.</p> <p>5 Q. What chatter are you aware of?</p> <p>6 And what is chatter?</p> <p>7 A. It's discussion among -- within</p> <p>8 the scientific and healthcare community of</p> <p>9 things that are on the drawing board for</p> <p>10 IARC.</p> <p>11 Q. Do you know whether or not</p> <p>12 IARC -- well, strike that.</p> <p>13 IARC has not changed its</p> <p>14 position that the migration theory and</p> <p>15 evidence for the migration theory is weak; is</p> <p>16 that right?</p> <p>17 MS. O'DELL: Object to the</p> <p>18 form.</p> <p>19 A. They have not changed their</p> <p>20 position that was published in the 2010</p> <p>21 monograph.</p> <p>22 BY MR. ZELLERS:</p> <p>23 Q. All right. You have heard</p> <p>24 chatter that they may look at it again; is</p>
<p style="text-align: right;">Page 203</p> <p>1 they?</p> <p>2 A. No.</p> <p>3 Q. Are you aware that that IARC --</p> <p>4 and you're familiar with IARC, right?</p> <p>5 A. Yes.</p> <p>6 Q. Are you aware that IARC rejects</p> <p>7 this migration theory and calls the evidence</p> <p>8 weak?</p> <p>9 MS. O'DELL: Object to the</p> <p>10 form.</p> <p>11 A. The IARC has made that</p> <p>12 statement in their -- I think the 2006 review</p> <p>13 that resulted in their recent monograph, but</p> <p>14 I think they're about to reconsider that.</p> <p>15 BY MR. ZELLERS:</p> <p>16 Q. Well, they also have stated</p> <p>17 that in 2010; is that right?</p> <p>18 A. Well, that's the --</p> <p>19 MS. O'DELL: Object to the</p> <p>20 form.</p> <p>21 A. That's the monograph from the</p> <p>22 2006 review.</p> <p>23 BY MR. ZELLERS:</p> <p>24 Q. Why do you believe that they're</p>	<p style="text-align: right;">Page 205</p> <p>1 that right?</p> <p>2 A. Yes.</p> <p>3 Q. Other than this chatter, you're</p> <p>4 unaware of any other -- well, strike that.</p> <p>5 You're unaware of any change in</p> <p>6 IARC's position with respect to migration,</p> <p>7 correct?</p> <p>8 A. Well, an example of what I'm</p> <p>9 talking about is the Health Canada report,</p> <p>10 which has contradicted what is found in the</p> <p>11 IARC monograph and is more current and</p> <p>12 considers information that will probably go</p> <p>13 into the next IARC review.</p> <p>14 MR. ZELLERS: Move to strike as</p> <p>15 nonresponsive.</p> <p>16 BY MR. ZELLERS:</p> <p>17 Q. Does IARC review and rely on</p> <p>18 draft assessments in formulating their</p> <p>19 positions?</p> <p>20 A. IARC relies on primary studies.</p> <p>21 Q. Not draft assessments, correct?</p> <p>22 A. Well, the draft assessment that</p> <p>23 I guess you're referring to, the Health</p> <p>24 Canada draft assessment, is derived from</p>

<p style="text-align: right;">Page 206</p> <p>1 primary studies, the same ones that will be 2 considered by IARC.</p> <p>3 Q. All right. As of today, IARC's 4 published position is that evidence of a 5 migration theory of talcum powder migrating 6 to the ovaries is weak, correct?</p> <p>7 A. Yes.</p> <p>8 Q. Have you conducted any tests or 9 experiments with respect to your theory or 10 position that talc migrates to the ovaries 11 through the reproductive tract?</p> <p>12 A. No, I haven't.</p> <p>13 Q. How much talc actually reaches 14 the ovaries in your opinion?</p> <p>15 A. I can't answer that question 16 because the dose has not been quantified.</p> <p>17 Q. Does it only reach the ovaries 18 during certain times?</p> <p>19 A. I don't believe so. I think 20 there are many circumstances whereby that 21 migration pathway is functional, and in my 22 belief, the pathway from the perineum to the 23 cervix is pretty much an open channel, and 24 then it continues to be open pretty much all</p>	<p style="text-align: right;">Page 208</p> <p>1 is that right?</p> <p>2 A. That is correct.</p> <p>3 Q. You are not one of those 4 physicians, correct?</p> <p>5 A. I don't claim to be a 6 specialist in gynecology.</p> <p>7 Q. Your third opinion is that the 8 ovaries lack an intrinsic elimination system; 9 is that right?</p> <p>10 A. That's correct.</p> <p>11 Q. Is "intrinsic elimination 12 system" a recognized term of art that's used 13 by gynecologists?</p> <p>14 A. I don't think so. It was just 15 the term I used to describe the situation.</p> <p>16 Q. Is "intrinsic elimination 17 system" a term of art used by oncologists?</p> <p>18 A. The same answer.</p> <p>19 Q. Have you seen published studies 20 that use that term?</p> <p>21 A. I don't know. I suspect I 22 could have. It's apparently a small number 23 of ways to describe that in a few words.</p> <p>24 Q. You do not cite to any studies</p>
<p style="text-align: right;">Page 207</p> <p>1 the way into the pelvic cavity.</p> <p>2 Q. You are not a specialist in 3 women's health issues, correct?</p> <p>4 MS. O'DELL: Object to the 5 form.</p> <p>6 A. Well, I'm a doctor. I've 7 examined a lot of women.</p> <p>8 BY MR. ZELLERS:</p> <p>9 Q. Are you --</p> <p>10 MS. O'DELL: Excuse me. Are 11 you finished, sir?</p> <p>12 THE WITNESS: Yes, I'm 13 finished.</p> <p>14 MS. O'DELL: Okay.</p> <p>15 BY MR. ZELLERS:</p> <p>16 Q. Are you an expert in the 17 women's reproductive tract?</p> <p>18 A. I've taken it apart and put it 19 back together again in medical school, and in 20 other settings I've done OB/GYN rotations. 21 I've participated in pelvic surgeries. I 22 understand the anatomy.</p> <p>23 Q. There are physicians who are 24 specialists in the female reproductive tract;</p>	<p style="text-align: right;">Page 209</p> <p>1 in the body of your report to support your 2 theory that the ovaries do not have an 3 intrinsic elimination system, correct?</p> <p>4 A. That's correct.</p> <p>5 Q. You have not conducted any 6 tests to show that exposure to the ovaries to 7 particulate matter, if any, is longer than 8 exposure to other parts of the female 9 anatomy; is that right?</p> <p>10 MS. O'DELL: Object to the 11 form.</p> <p>12 A. I have not conducted any such 13 tests.</p> <p>14 BY MR. ZELLERS:</p> <p>15 Q. Is the cervix more or less 16 sensitive to the impact of foreign particles 17 than the ovaries?</p> <p>18 MS. O'DELL: Object to the 19 form.</p> <p>20 A. I think that the important 21 point is the residence time that exists, and 22 the cervix is not presented with things for 23 an extended time like the ovaries are in 24 relation to things like talc. But it is</p>

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1 sensitive.
 2 BY MR. ZELLERS:
 3 Q. All right. Your fourth
 4 theory -- or strike that.
 5 Your fourth opinion is that the
 6 epidemiological studies show a positive
 7 relationship between regular perineal
 8 application of talcum powder and ovarian
 9 cancer; is that right?
 10 A. That's correct.
 11 Q. The studies that you reference
 12 in this opinion are referred to on pages 6
 13 and 7 of your report; is that right?
 14 MS. O'DELL: Object to the
 15 form.
 16 A. Most of them, yes.
 17 BY MR. ZELLERS:
 18 Q. You conclude that when
 19 confounding and bias are exhaustively
 20 considered -- and do you believe you've done
 21 that here?
 22 A. I am restating what authors of
 23 the primary studies have done. I'm
 24 evaluating the consistency of the evidence,

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1 not the basic evidence itself.
 2 Q. The apparent cause and effect
 3 relationship between perineal talcum powder
 4 use and ovarian cancer amounts to about a 30%
 5 increased risk of ovarian cancer in talcum
 6 powder users.
 7 Is that your opinion in this
 8 case?
 9 A. It is.
 10 Q. And that is your opinion from
 11 reviewing the epidemiologic studies that you
 12 cite in your report?
 13 A. Yes.
 14 Q. When epidemiologists refer to
 15 the statistical power of a study, what are
 16 they referring to?
 17 A. Statistical power refers to the
 18 ability of a study design, if carried out, to
 19 detect a signal in the data of a particular
 20 magnitude.
 21 Q. In plain English, statistical
 22 power is the likelihood that a study will
 23 detect an effect when there is an effect to
 24 be detected; is that fair?

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1 A. Yes.
 2 MS. O'DELL: Object to the
 3 form.
 4 BY MR. ZELLERS:
 5 Q. Are you familiar with the term
 6 "person-years" as it relates to
 7 epidemiological study?
 8 A. Yes, I am.
 9 Q. What is -- strike that.
 10 How are person-years
 11 calculated?
 12 A. They are calculated by -- in
 13 relation to an exposure or to an existing
 14 treatment, they're calculated by multiplying
 15 the duration of the treatment or exposure in
 16 years by the number of people being studied.
 17 And that -- the result is person-years.
 18 Q. Can you explain the difference
 19 between high-grade serous and low-grade
 20 serous cancer?
 21 A. High-grade serous cancer has
 22 a -- is less differentiated and has a greater
 23 propensity for metastasis and invasion.
 24 Q. Are you aware that the

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1 epidemiological literature shows that these
 2 are very different cancers?
 3 A. They behave quite differently,
 4 yes.
 5 Q. Do you know what publication
 6 bias is?
 7 A. Yes.
 8 Q. What is publication bias?
 9 A. Publication bias is the
 10 tendency to -- to spin a certain argument
 11 in -- in order to influence acceptance of
 12 publications.
 13 Q. Is that a recognized issue in
 14 the field of epidemiology, at least as you've
 15 observed?
 16 A. It's a -- it's not necessarily
 17 recognized in the field of epidemiology. It
 18 exists in all scientific endeavors.
 19 Q. Is it something that you and
 20 other physicians and experts and scientists
 21 need to be aware of?
 22 A. Yes. I think we're all exposed
 23 to the effects of that and warned about it as
 24 we go through our careers.

<p style="text-align: right;">Page 214</p> <p>1 Q. When I asked you early on what 2 your methodology was, you looked at the 3 published literature, you looked at some 4 websites I think that you told us about 5 earlier, and then you performed a risk 6 assessment and considered whether perineal 7 use of talc products poses a safety risk to 8 consumers; is that right?</p> <p>9 MS. O'DELL: Object to the 10 form.</p> <p>11 A. Well, that's a gross 12 oversimplification of the risk assessment 13 process that I performed.</p> <p>14 The review of the literature, 15 which was based on the question that I was 16 asked to address, was a fairly exhaustive one 17 which incorporated a search for every 18 pertinent publication that was available and 19 included multiple languages.</p> <p>20 It then was -- proceeded into a 21 distillation of the facts that were -- that 22 were claimed based on those individual 23 studies and investigations, and a comparison 24 of those, one with another, eventually</p>	<p style="text-align: right;">Page 216</p> <p>1 been published as well. And I felt that was 2 sufficient to be able to produce this report 3 that addressed the question I was asked.</p> <p>4 Q. As you told us earlier, you 5 have never published a meta-analysis on any 6 topic; is that right?</p> <p>7 A. That's correct.</p> <p>8 Q. You cite to some of the 9 available studies on talcum powder use in 10 ovarian cancer, but not to all of the 11 studies, correct?</p> <p>12 MS. O'DELL: Object to the 13 form.</p> <p>14 A. That's true.</p> <p>15 BY MR. ZELLERS:</p> <p>16 Q. What was your reasoning for 17 focusing on certain studies and excluding 18 other studies?</p> <p>19 A. The studies that I referenced 20 were those that had specific aspects that 21 directly influenced my report or my 22 conclusions or that I felt were illustrative 23 of comments I was making in the report, and 24 that's why they were referenced.</p>
<p style="text-align: right;">Page 215</p> <p>1 considering them all as a whole to arrive at 2 conclusions that addressed the question.</p> <p>3 BY MR. ZELLERS:</p> <p>4 Q. That was your methodology; is 5 that right?</p> <p>6 A. That is the methodology, yes.</p> <p>7 Q. Did you consider the Bradford 8 Hill criteria or factors in reaching your 9 conclusions and opinions in this matter?</p> <p>10 A. That's part of the methodology 11 which is outlined in my report.</p> <p>12 Q. In analyzing the Bradford Hill 13 criteria, did you conduct a meta-analysis of 14 the available data to reach a conclusion 15 about the relative risk?</p> <p>16 A. No, I did not.</p> <p>17 Q. Why didn't you conduct a 18 meta-analysis for this case?</p> <p>19 A. I did not have the time to do a 20 meta-analysis in this case, first of all. 21 Secondly, there have been a number of other 22 meta-analyses performed, and I had those 23 results available to me in addition to 24 various reviews of the literature that have</p>	<p style="text-align: right;">Page 217</p> <p>1 All of the studies may not have 2 risen to that -- the level of requiring being 3 referenced, but pretty much all the studies 4 are included in the literature that I 5 reviewed.</p> <p>6 Q. You cite in the report the 7 studies that were favorable or supportive of 8 your opinions, correct?</p> <p>9 A. Well, I cited a number of 10 studies, not all of which were favorable to 11 my overall opinions, at least not on the 12 surface.</p> <p>13 Q. Did you cite all of the studies 14 that you believe in one way or another 15 support your opinions in this case?</p> <p>16 A. I don't think so.</p> <p>17 Q. You believe there are 18 additional studies that support your opinions 19 that you did not cite?</p> <p>20 A. They're in the literature list.</p> <p>21 Q. Did you cite the opinions that 22 refuted -- strike that.</p> <p>23 Did you cite the studies that 24 refuted your opinions in this matter?</p>

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1 A. I cited some studies that had
2 opinions that -- or that had conclusions that
3 did not necessarily agree with mine, but I
4 don't think they refuted my conclusions.

5 Q. Do you believe the standard for
6 proving causation in the scientific
7 literature is the same one that applies in
8 this litigation?

9 MS. O'DELL: Object to the
10 form.

11 A. I don't know that.

12 BY MR. ZELLERS:

13 Q. A document you brought here
14 today was an FDA letter?

15 A. Yeah, I think you marked it.

16 Q. I did mark it. Why don't you
17 see if you could find it so I can ask you a
18 couple of questions about it.

19 A. There it is. That one?

20 Q. Yes. Exhibit 10 is an FDA
21 letter dated April 1st of 2014 to a
22 Dr. Epstein; is that right?

23 A. Yes.

24 Q. That is a document that you

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1 reviewed and considered as part of your
2 analysis of this case; is that right?

3 A. Yes.

4 Q. Do you believe that that
5 exhibit, Exhibit 10, is supportive of your
6 opinions in this matter?

7 A. I don't think it's very
8 supportive. It's -- it's in response to a
9 proposal from a citizens voluntary agency to
10 provide more stringent labeling on talcum
11 powder products, and the agency rejected
12 the -- that petition.

13 Q. The FDA is the regulatory body
14 in the United States that oversees food, drug
15 and cosmetics; is that right?

16 MS. O'DELL: Object to the
17 form.

18 A. Yes.

19 BY MR. ZELLERS:

20 Q. This letter -- strike that.

21 In this letter the FDA goes
22 through and analyzes some of the Bradford
23 Hill factors; is that right?

24 A. I'd have to look at this in

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1 more detail to be able to answer that
2 specifically.

3 Q. Well, essentially, based upon
4 its analysis as of 2014, the FDA concluded
5 that causation had not been established as
6 between genital talcum powder use and ovarian
7 cancer or an increased risk of ovarian
8 cancer, correct?

9 A. Well, it said that an updated
10 review failed to identify any new compelling
11 literature data or new scientific evidence.
12 I don't think they indicate here that they
13 actually did a standard review of that
14 literature.

15 Q. Well, take a look, if you will,
16 at page 4. The FDA sets forth its
17 epidemiology and etiology findings; is that
18 right?

19 A. Yes.

20 Q. The FDA has a number of very
21 capable physicians, scientists,
22 toxicologists, pharmacologists and medical
23 professionals; is that right?

24 MS. O'DELL: Object to the

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1 form.

2 A. I don't know if they're still
3 working, but they have good people on staff.
4 BY MR. ZELLERS:

5 Q. And just so, a year or two or
6 three, if this transcript is ever reviewed,
7 we are in the midst of a shutdown of at least
8 portions of the government; is that right?

9 A. That's correct.

10 Q. And that is what your comment
11 was directed to, correct?

12 A. That is correct.

13 Q. On page 4 the FDA states:

14 After consideration of the scientific
15 literature submitted in support of both
16 citizens' petitions, FDA found.

17 And then, number 2, that
18 several of the studies acknowledge biases in
19 the study design and no single study has
20 considered all the factors that potentially
21 contribute to ovarian cancer, including
22 selection bias and/or uncontrolled
23 confounding that result in spurious positive
24 associations between talc use and ovarian

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1 cancer risk.

2 Did I read that correctly?

3 A. You did read it correctly.

4 Q. Does that appear to be at least
5 one of the conclusions of the FDA after
6 considering the scientific literature as of
7 early 2014?

8 MS. O'DELL: Object to the
9 form.

10 A. Yes, that is listed as an FDI
11 finding -- FDA finding.

12 BY MR. ZELLERS:

13 Q. The FDA noted that a
14 dose-response -- strike that.

15 The FDA noted that
16 dose-response evidence is lacking; is that
17 right?

18 A. A dose-response --

19 Q. Two things. The FDA notes that
20 there's a lack of consistency in the study
21 results, correct?

22 MS. O'DELL: Where are you
23 reading? I'm sorry.

24 MR. ZELLERS: I'm looking at

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1 Conclusion 3.

2 THE WITNESS: Point 3.

3 A. They found that the
4 case-control studies did not demonstrate a
5 consistent positive association across
6 studies; although some studies have found
7 small positive associations between talc and
8 ovarian cancer, but lower confidence limits
9 are often close to 1, and dose-response
10 evidence is lacking.

11 BY MR. ZELLERS:

12 Q. That was FDA's conclusion
13 number 3 based upon its review of the
14 scientific literature; is that right?

15 MS. O'DELL: Object to the
16 form.

17 A. It's correct. It's not a valid
18 interpretation of the statistical results,
19 but that was one of their findings.

20 BY MR. ZELLERS:

21 Q. Well, that was their finding.
22 You disagree at least in part with their
23 finding; is that right?

24 MS. O'DELL: Object to the

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1 form.

2 A. That is correct.

3 BY MR. ZELLERS:

4 Q. You are a paid expert for the
5 plaintiffs in this litigation; is that right?

6 A. That is correct.

7 Q. To your knowledge, the FDA is
8 not paid -- well, let me withdraw that.

9 A. I wouldn't go out on a limb
10 there.

11 Q. Number 4, Conclusion 4, a
12 cogent biological mechanism by which talc
13 might lead to ovarian cancer is lacking.
14 Exposure to talc does not account for all
15 cases of ovarian cancer and there was no
16 scientific consensus on the proportion of
17 ovarian cancer cases that may be caused by
18 talc exposure.

19 Was that a conclusion of the
20 FDA based upon its review of the
21 epidemiologic literature?

22 MS. O'DELL: Object to the
23 form.

24 A. Yes, it was, and it's one that

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1 I also disagree with.

2 BY MR. ZELLERS:

3 Q. IARC also considered the
4 Bradford Hill considerations; is that right?

5 A. Yes, it did.

6 Q. IARC rejected classification of
7 talc as a carcinogenic, instead assigning it
8 to the classification of possibly
9 carcinogenic to humans; is that correct?

10 A. That's correct.

11 Q. We've already discussed the
12 IARC categories briefly, but let's mark a
13 document from the IARC website as to the
14 classifications, Exhibit 21.

15 (Carson Deposition Exhibit 21
16 marked.)

17 BY MR. ZELLERS:

18 Q. Tell me if you recognize that.

19 A. Yes.

20 Q. Exhibit 21 is from the IARC
21 website, and it goes through the
22 classifications of different agents that have
23 been made by the International Agency for
24 Research on Cancer; is that right?

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1 A. Yes, that's correct.

2 Q. It has studied and included 120

3 agents in the Group 1 category, which is

4 carcinogenic to humans, correct?

5 A. That's correct.

6 Q. That's the only category in

7 which IARC finds sufficient evidence in

8 humans, correct?

9 MS. O'DELL: Object to the

10 form.

11 A. That's the category that

12 represents substances for which there is

13 sufficient and irrefutable evidence of human

14 carcinogenesis.

15 BY MR. ZELLERS:

16 Q. It lists 82 agents in Group 2A

17 as being probably carcinogenic to humans; is

18 that right?

19 A. That's correct.

20 Q. IARC is certainly willing to

21 declare agents as either a known or probable

22 carcinogen; is that right?

23 A. That's correct.

24 Q. There is only one agent in

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1 Group 4, probably not carcinogenic to humans,

2 correct?

3 A. Yes. I thought that number had

4 gone up recently, but the date here is

5 November 2018, so some may have been moved

6 back into Group 3.

7 Q. So out of the over 1,000 agents

8 that IARC has reviewed, it's only placed one

9 agent in the Group 4 category, probably not

10 carcinogenic; is that right?

11 A. That's correct.

12 Q. There is no Group 5, not

13 carcinogenic; is that right?

14 A. That's correct.

15 Q. With genital talc, IARC

16 Group 2B designation -- well, strike that.

17 Genital talc is listed as an

18 IARC Group 2B designated substance; is that

19 right?

20 A. That's correct.

21 Q. That's based on limited

22 evidence in humans, which means that IARC

23 cannot rule out chance, bias or confounding

24 with reasonable confidence, correct?

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1 MS. O'DELL: Object to the

2 form.

3 A. I think limited evidence also

4 refers to just the number of studies that

5 have been performed as well as the quality of

6 the studies.

7 BY MR. ZELLERS:

8 Q. Well, based upon the evidence

9 that is available, the studies that are

10 available, a 2B designation by IARC means

11 that IARC cannot rule out chance, bias or

12 confounding with reasonable confidence,

13 correct?

14 MS. O'DELL: Objection, asked

15 and answered.

16 A. Not always the case.

17 BY MR. ZELLERS:

18 Q. That's part of the definition,

19 isn't it?

20 A. I don't believe it applies to

21 every agent or every evaluation.

22 Q. Well, I'll not take the time to

23 go through the IARC definitions; if we at the

24 end of the day have extra time, we'll go back

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1 and we'll take a look.

2 What else is in the Class 2B,

3 possibly carcinogenic. Ginkgo biloba, is

4 that something you're aware of that's in that

5 category?

6 MS. O'DELL: Object to the

7 form.

8 A. That's a biological material.

9 BY MR. ZELLERS:

10 Q. Pickled vegetables?

11 A. That may be in Group 2B.

12 Q. Occupational carpentry and

13 joinery?

14 MS. O'DELL: Objection to form.

15 A. That's wood dust exposure.

16 BY MR. ZELLERS:

17 Q. Also 2B; is that right?

18 A. Wood dust itself is Group 1.

19 The occupation is Group 2B.

20 Q. Let me ask you about some

21 individual Bradford Hill criteria. On

22 page 10 of your report, you state that you

23 gave the most weight to strength of

24 association, consistency and biologic

Page 230

1 plausibility; is that right?
 2 A. That's correct.
 3 Q. How much weight did you give to
 4 the other six factors?
 5 A. Sufficient.
 6 Q. Why did you put less weight on
 7 those?
 8 A. Because the strength of
 9 association, the consistency of the evidence
 10 and the biological plausibility of perineal
 11 talc, talcum powder application as
 12 responsible for the occurrence of ovarian
 13 cancer was compelling.
 14 Q. FDA focused on dose, correct?
 15 A. Yes.
 16 Q. You did not; is that right?
 17 A. That's right.
 18 Q. The first Bradford Hill factor
 19 that you focused on was strength of
 20 association.
 21 What association does the
 22 literature report between talc use and
 23 ovarian cancer?
 24 A. Overall, evaluating the

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1 universe of research, epidemiologic research
 2 that's been done on this, it shows an average
 3 30% increase in ovarian cancer risk for those
 4 who regularly apply talcum powder to the
 5 perineum.
 6 Q. Regular application of talcum
 7 powder means what?
 8 A. It -- I believe that it means
 9 daily or thereabouts.
 10 Q. In what form of application?
 11 A. Talcum powder.
 12 Q. In what amount?
 13 A. Whatever is necessary or
 14 desired by the user.
 15 Q. Does that vary from woman to
 16 woman?
 17 A. It does.
 18 Q. Did you make any attempt to
 19 assess what regular use of talcum powder was?
 20 MS. O'DELL: Object to the
 21 form.
 22 A. There have been a couple of
 23 attempts to try to quantify what -- what that
 24 means. I think for the most part they've

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1 been failed attempts, but they have been
 2 attempts to estimate the quantity of powder
 3 that you start with and the amount that
 4 results in the application to the perineum by
 5 using models and actually doing some
 6 measurements and recording activities.
 7 BY MR. ZELLERS:
 8 Q. You did not do any modeling or
 9 any assessment of the quantity of baby powder
 10 that was involved with daily use; is that
 11 right?
 12 A. No, I relied on those others.
 13 Q. When you say 30% increased
 14 risk, that's a 1.3 odds ratio; is that right?
 15 A. That's correct.
 16 Q. And that comes largely from the
 17 case-control studies, correct?
 18 MS. O'DELL: Object to the
 19 form.
 20 A. Yes, but it's also consistent
 21 with some of the information from the cohort
 22 studies.
 23 BY MR. ZELLERS:
 24 Q. Epidemiologists consider a 1.3

Page 233

1 odds ratio in a case-control study to be a
 2 weak or modest association; is that right?
 3 MS. O'DELL: Object to the
 4 form.
 5 A. That's correct.
 6 BY MR. ZELLERS:
 7 Q. Where here we're talking only
 8 about statistical associations, not
 9 causation, correct?
 10 MS. O'DELL: Object to the
 11 form.
 12 A. Well, association eventually
 13 becomes causation when the -- when the
 14 evidence mounts to a point where it becomes
 15 recognized by all of the players that this is
 16 what's going on.
 17 A 30% increase may be
 18 classified by epidemiologists as weak or
 19 modest, but if you look at the number of
 20 women in this country who die each year from
 21 this fatal disease, that represents about
 22 3,000 lives that could potentially be saved
 23 through prevention.
 24 Q. There is not a --

<p style="text-align: right;">Page 234</p> <p>1 MS. BOCKUS: Excuse me, I need 2 to object as nonresponsive. 3 MR. ZELLERS: Yes, join. 4 BY MR. ZELLERS: 5 Q. There is not a consensus at 6 this time with respect to any causation 7 relating to genital talc and ovarian cancer, 8 is there? 9 MS. O'DELL: Objection to the 10 form. 11 A. I believe that that consensus 12 is building. 13 BY MR. ZELLERS: 14 Q. FDA -- that's not FDA's 15 position, correct? 16 MS. O'DELL: Object to the 17 form. 18 A. Not at the moment. 19 BY MR. ZELLERS: 20 Q. That's not the position of the 21 National Cancer Institute; is that right? 22 A. That's correct. 23 Q. That's not the position of the 24 CDC; is that correct?</p>	<p style="text-align: right;">Page 236</p> <p>1 epidemiologists are concerned, correct? 2 MS. O'DELL: Object to -- 3 object to the form. 4 A. It's an increased risk that 5 translates into human lives, so it depends on 6 your point of view. 7 MS. BOCKUS: Object to form -- 8 I mean, sorry, nonresponsive, move to 9 strike. 10 MR. ZELLERS: Join. 11 MS. O'DELL: Oppose. 12 DR. THOMPSON: Agreed. 13 BY MR. ZELLERS: 14 Q. The 1.3 relative risk that you 15 believe generally applies, that would relate 16 to epithelial cancers; is that right? 17 A. Yes. 18 Q. That's what you're limiting 19 your opinions to in this case, correct? 20 MS. O'DELL: Object to the 21 form. 22 A. Well, these opinions relate to 23 several of the cancers that have shown 24 increases in these background epidemiologic</p>
<p style="text-align: right;">Page 235</p> <p>1 A. That's correct. 2 Q. IARC does not refer to any 3 association between perineal talc use and 4 ovarian cancer as a strong association, does 5 it? 6 MS. O'DELL: Object to the 7 form. 8 A. It calls it a Group 2B 9 carcinogen, which is fairly significant. 10 BY MR. ZELLERS: 11 Q. Well, we discussed a few 12 minutes ago that if an agent is a Group 2B 13 carcinogen, that is based on limited evidence 14 in humans; is that right? 15 A. That's correct. 16 Q. All right. Your opinions on 17 strength of association, do they apply 18 equally to all forms of ovarian cancer? 19 A. No, they don't. These apply to 20 the epithelial ovarian cancer spectrum. 21 Q. Your opinions in terms of there 22 being a -- well, let me withdraw that. 23 We've agreed that 1.3 is not a 24 strong association, at least insofar as</p>	<p style="text-align: right;">Page 237</p> <p>1 studies, which include the epithelial ovarian 2 cancers, including the serous; the borderline 3 cancers are also showing increases in some of 4 the studies. So it's the group of those 5 cancers, yes. 6 BY MR. ZELLERS: 7 Q. The cohort studies, prospective 8 cohort studies, have not shown an association 9 between talc and ovarian cancer, correct? 10 MS. O'DELL: Object to the 11 form. 12 A. They have in some subtypes. 13 BY MR. ZELLERS: 14 Q. There was an initial 15 description with respect to the first Nurses' 16 study that was not supported in the update of 17 that study; is that correct? 18 A. The Nurses' Health Study? 19 Q. Yes. 20 A. Yes, that's correct. 21 Q. Let's look at a different 22 criteria, consistency. The literature does 23 not show a consistent association between 24 talc use and ovarian cancer, correct?</p>

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<p>1 MS. O'DELL: Object to the</p> <p>2 form.</p> <p>3 A. I believe that, in fact,</p> <p>4 research shows -- does show a consistent</p> <p>5 pattern.</p> <p>6 BY MR. ZELLERS:</p> <p>7 Q. The cohort studies do not show</p> <p>8 an association between talc use and ovarian</p> <p>9 cancer as we just discussed, correct?</p> <p>10 A. The basic cohort studies that</p> <p>11 look at all of the subjects and all of the</p> <p>12 cancers together typically do not rise to the</p> <p>13 level of significance.</p> <p>14 Q. The hospital-based case-control</p> <p>15 studies collectively do not show an</p> <p>16 association between talc use and ovarian</p> <p>17 cancer, correct?</p> <p>18 A. I sort of discount the</p> <p>19 distinction between the hospital-based</p> <p>20 studies and the community-based studies. I'm</p> <p>21 not sure whether there are valid reasons to</p> <p>22 consider those differently.</p> <p>23 Q. We've discussed earlier that</p> <p>24 you are not an epidemiologist; is that right?</p>	<p>1 ill patients in the community to healthy</p> <p>2 people in the community, correct?</p> <p>3 A. In some cases that might be</p> <p>4 correct, but I'm not sure that's any -- in</p> <p>5 any sort of world an advantage.</p> <p>6 Q. Well, shouldn't there be</p> <p>7 consistency if the Bradford Hill criteria is</p> <p>8 to be -- well, strike that.</p> <p>9 In applying the Bradford Hill</p> <p>10 criteria of consistency, there should be</p> <p>11 consistency across different types of</p> <p>12 studies, cohort studies, hospital-based</p> <p>13 case-control studies, and population-based</p> <p>14 case-control studies, correct?</p> <p>15 MS. O'DELL: Object to the</p> <p>16 form.</p> <p>17 A. That's correct.</p> <p>18 BY MR. ZELLERS:</p> <p>19 Q. Isn't the absence of an</p> <p>20 association in the cohort studies especially</p> <p>21 significant in that the study design for the</p> <p>22 cohort studies reduces the likelihood of</p> <p>23 recall bias?</p> <p>24 A. There are many forms of bias</p>
Page 239	Page 241
<p>1 MS. O'DELL: Object to the</p> <p>2 form, misstates his testimony.</p> <p>3 A. I don't think I necessarily</p> <p>4 agreed to that characterization because I</p> <p>5 deal a lot with epidemiologic work. I'm a</p> <p>6 faculty member in the Department of</p> <p>7 Epidemiology at the University of Texas</p> <p>8 School of Public Health, and some may</p> <p>9 consider me an epidemiologist.</p> <p>10 BY MR. ZELLERS:</p> <p>11 Q. Do you consider yourself an</p> <p>12 expert in epidemiology?</p> <p>13 A. No.</p> <p>14 Q. Do you agree -- well, do you</p> <p>15 agree that hospital-based case-control</p> <p>16 studies are less susceptible to selection</p> <p>17 bias than population-based case-control</p> <p>18 studies?</p> <p>19 A. It depends on the methodology</p> <p>20 that's used to recruit the study subjects.</p> <p>21 Q. With hospital-based</p> <p>22 case-controlled studies, you're more likely</p> <p>23 to be comparing hospitalized patients to</p> <p>24 hospitalized patients rather than comparing</p>	<p>1 that study designers need to consider in the</p> <p>2 process of designing a study, and there are</p> <p>3 even more types of bias that are discovered</p> <p>4 after a study has begun.</p> <p>5 You can fault case-control</p> <p>6 studies for being particularly sensitive to</p> <p>7 recall bias, but many of these authors who</p> <p>8 perform these studies indicated that they</p> <p>9 were well aware of that bias potential and</p> <p>10 took measures to avoid it.</p> <p>11 The same thing can be said</p> <p>12 about cohort studies. They suffer from other</p> <p>13 forms of bias, misclassification in</p> <p>14 particular. They may also suffer from the</p> <p>15 fact that they are extremely expensive, have</p> <p>16 long duration, and require very large numbers</p> <p>17 of subjects in order to carry them out and</p> <p>18 are frequently underpowered and unable to</p> <p>19 arrive at the conclusions that they seek for</p> <p>20 that reason.</p> <p>21 MR. ZELLERS: Move to strike as</p> <p>22 nonresponsive.</p> <p>23 BY MR. ZELLERS:</p> <p>24 Q. Is it possible that recall bias</p>

<p style="text-align: right;">Page 242</p> <p>1 explains the difference between the cohort 2 studies and the retrospective case-control 3 studies? 4 MS. O'DELL: Object to form, 5 asked and answered. 6 A. I don't believe that that is 7 the case. 8 BY MR. ZELLERS: 9 Q. Is it possible? 10 MS. O'DELL: Objection. 11 A. Theoretically it would be 12 possible. 13 BY MR. ZELLERS: 14 Q. Are you familiar with the 15 Berge -- Berge 2017 study? 16 A. Yes. 17 Q. Is that a study that you cite 18 and reviewed and rely on? 19 A. It was a meta-analysis. 20 Q. Is that a meta-analysis that 21 you cite, review and have relied upon? 22 A. Yes. 23 Q. Take a look, if you will, at 24 Exhibit 22.</p>	<p style="text-align: right;">Page 244</p> <p>1 paragraph. Reading from the second full 2 paragraph, the authors discuss the fact that 3 the association between genital talc use and 4 risk of ovarian cancer is present in 5 case-control but not in cohort studies, can 6 be attributed to bias in the former type of 7 studies; is that right? 8 MS. O'DELL: Object to the 9 form. 10 A. That's what it says. 11 BY MR. ZELLERS: 12 Q. Then continuing down: 13 Information bias from retrospective 14 self-report of talc use is a possible 15 explanation for the association detected in 16 case-control studies. 17 Is that right? 18 A. That's what it says. 19 Q. What was your methodology for 20 discounting the effect of recall bias in the 21 population-based case-control studies? 22 A. The fact that several authors 23 discussed the possibility of recall bias and 24 incorporated methodology for avoiding recall</p>
<p style="text-align: right;">Page 243</p> <p>1 (Carson Deposition Exhibit 22 2 marked.) 3 THE WITNESS: Thank you. 4 MS. O'DELL: Thank you. 5 BY MR. ZELLERS: 6 Q. You're familiar with this 7 meta-analysis; is that right? 8 A. Yes. 9 Q. The authors conclude that 10 information bias from retrospective 11 self-report of talc use is a possible 12 explanation for the association detected in 13 case-control studies; is that right? 14 MS. O'DELL: I'm sorry, are you 15 reading from a certain page? 16 MR. ZELLERS: I am. 17 MS. O'DELL: Can you direct it 18 to us, please? 19 THE WITNESS: Could you tell us 20 where that is? 21 MR. ZELLERS: Sure. 22 BY MR. ZELLERS: 23 Q. Take a look if you will on 24 page 6, the right-hand column, third</p>	<p style="text-align: right;">Page 245</p> <p>1 bias, for example, placing parallel questions 2 that should be affected in the same way, and 3 still showed a positive result for talc and 4 ovarian cancer is one reason. 5 The other has to do with 6 consistency of the results, and although 7 you've stated that from these various 8 documents, including this quotation, that the 9 case-control studies showed positive 10 associations but the cohort studies did not, 11 I would -- I would refute that by saying that 12 all of the -- the vast majority of all of the 13 studies show a positive odds ratio or 14 relative risk, even if they don't rise to the 15 level of significance. 16 If these results were obtained 17 simply by chance, you would expect an equal 18 number of positive results and negative 19 results, but we don't have that here. We 20 have practically all positive results with 21 three or four outliers. 22 And so -- 23 Q. We looked at the Taher paper 24 early on in this deposition where Taher</p>

<p style="text-align: right;">Page 246</p> <p>1 concluded that 15 out of the 30 case-control 2 studies reported a statistically significant 3 association between genital talc use and 4 ovarian cancer, correct? 5 A. That's correct, but you're 6 not -- you're not talking about the other 15. 7 Q. The hospital-based case-control 8 studies collectively do not show a 9 statistically significant association between 10 talc use and ovarian cancer, correct? 11 MS. O'DELL: Object to the 12 form. 13 A. I don't know that that is the 14 case. 15 BY MR. ZELLERS: 16 Q. You don't know that it's not 17 the case; you'd have to go back and relook at 18 the studies, fair? 19 A. I'd have to look through here, 20 which I'm happy to do if you want me to, but 21 I don't believe that that's the case. 22 Q. In fact, the author, you cite 23 the Langseth paper, a 2008 paper, as 24 supportive of your position; is that right?</p>	<p style="text-align: right;">Page 248</p> <p>1 page. 2 MS. O'DELL: Object to the 3 form. 4 BY MR. ZELLERS: 5 Q. Is that the conclusion of the 6 authors? 7 A. What I'm reading here is on 8 balance, the epidemiological evidence 9 suggests that the use of cosmetic talc in the 10 perineal area may be associated with ovarian 11 cancer risk. The mechanism of 12 carcinogenicity may be related to 13 inflammation. 14 Q. Take a look at the paragraph on 15 the right-hand side under Proposal to 16 Research Community. I'm looking at the 17 second page of the Langseth article. 18 Are you there? 19 A. Yes, I am. 20 Q. The authors state: The current 21 body of experimental and epidemiological 22 evidence is insufficient to establish a 23 causal association between perineal use of 24 talc and ovarian cancer risk.</p>
<p style="text-align: right;">Page 247</p> <p>1 A. Yes. 2 Q. I'll mark that 3 Deposition Exhibit 23. 4 A. I think it was 2004, was it 5 not? 6 Q. Well, I'm going to hand it to 7 you and we can look at it together. 8 (Carson Deposition Exhibit 23 9 marked.) 10 A. Okay. 11 BY MR. ZELLERS: 12 Q. You're familiar with the 13 Langseth paper; is that right? 14 A. Yes. 15 (Comments off the stenographic 16 record.) 17 BY MR. ZELLERS: 18 Q. Langseth and the authors 19 concluded that the current body of 20 experimental and epidemiological evidence is 21 insufficient to establish a causal 22 association between perineal use of talc and 23 ovarian cancer risk; is that right? 24 And I'm looking at the second</p>	<p style="text-align: right;">Page 249</p> <p>1 Is that right? 2 MS. O'DELL: Object to the 3 form. 4 A. That's what it says. 5 BY MR. ZELLERS: 6 Q. Experimental research is needed 7 to better characterize deposition, retention 8 and clearance of talc to evaluate the ovarian 9 carcinogenicity of talc. 10 Is that what the authors state? 11 A. Well, that's what it says, but 12 it says much more. In fact, the editors of 13 the journal, in the section on the next page 14 that is titled What This Study Adds, say: 15 Epidemiological evidence suggests that the 16 use of cosmetic talc in the perineal area may 17 be associated with ovarian cancer risk. The 18 IARC has classified this use of talc as 19 possibly carcinogenic to human beings, 20 Group 2B. The mechanism of carcinogenicity 21 may be related to inflammation. This paper 22 focused on the high degree of consistency in 23 the studies accomplished so far and what 24 should be the focus in future studies.</p>

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1 So I --

2 Q. And then the conclusion is what
3 I read, that: The current body of
4 experimental and epidemiological evidence is
5 insufficient to establish a causal
6 association between perineal use of talc and
7 ovarian cancer risk.

8 Correct?

9 MS. O'DELL: Object to the
10 form.

11 A. That is what it says, but this
12 was accepted in 2007, which was now 12 years
13 ago.

14 BY MR. ZELLERS:

15 Q. Let me ask you about the cohort
16 studies. They involved a much greater number
17 of women than the case-controlled studies; is
18 that right?

19 MS. O'DELL: Object to the
20 form.

21 A. Well, they did not involve more
22 cases, but they involved more women because
23 in order to do a cohort study, you have to
24 start with a huge group of people and wait

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1 for them to develop cancers, and then count
2 those cancers.

3 BY MR. ZELLERS:

4 Q. What was your methodology for
5 weighing the power of the cohort studies
6 versus the case-control studies?

7 A. The cohort studies, it wasn't
8 apparent in every research report exactly how
9 they had done their sample size calculations
10 and power determinations, but in many cases
11 the lack of arriving at conclusions was
12 simply due to an inability to detect an
13 effect in the cohort studies, not that they
14 detected that there was not an effect. And
15 that's unfortunately a disadvantage of an
16 underpowered study.

17 Q. Is it your testimony that the
18 cohort studies are underpowered?

19 A. I think by and large most
20 cohort studies are underpowered and --
21 because power calculations are based on
22 chance. Investigators are sort of spinning
23 the roulette wheel and hoping that the number
24 that they want comes up. In some cases that

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1 doesn't happen.

2 Q. Is it your testimony that the
3 cohort studies relating to genital talc use
4 and ovarian cancer are spinning the roulette
5 wheel?

6 MS. O'DELL: Object to the
7 form.

8 A. In terms of the power of the
9 studies to detect a meaningful difference
10 among the subjects, yes.

11 BY MR. ZELLERS:

12 Q. That's your testimony as an
13 expert in this case; is that right?

14 A. It is my testimony that cohort
15 studies, including these, are chronic -- or
16 quite often underpowered simply because of
17 the expense associated with performing these
18 studies.

19 Q. What analysis did you do to
20 conclude that the cohort studies in this
21 area, the four cohort studies, are
22 underpowered?

23 A. Like I just mentioned to you, I
24 read the studies and looked at their

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1 conclusions, and their conclusions were not
2 that the effect didn't exist, but they
3 couldn't detect it.

4 MR. ZELLERS: Let's go off the
5 record because we need to change our
6 tape.

7 THE VIDEOGRAPHER: We're off
8 the record at 3:06, end of Tape 3.
9 (Recess taken, 3:06 p.m. to
10 3:19 p.m.)

11 THE VIDEOGRAPHER: We're on the
12 record at 3:19, beginning of Tape 4.

13 BY MR. ZELLERS:

14 Q. Dr. Carson, you are not a
15 statistician, correct?

16 A. That's correct.

17 Q. You are not a biostatistician;
18 is that right?

19 A. That's right.

20 Q. Do you agree that some of the
21 case-control studies have shown statistically
22 significant findings and others have not?

23 A. I do agree that.

24 Q. If a study does not show a

<p style="text-align: right;">Page 254</p> <p>1 statistically significant association, it 2 could mean that no risk exists, as we've 3 discussed; is that right? 4 A. That's correct. 5 Q. What methodology did you use to 6 weigh the lack of statistical significance 7 across studies? 8 MS. O'DELL: Object to the 9 form. 10 A. Across all of the case-control 11 studies? 12 BY MR. ZELLERS: 13 Q. Yes. 14 A. I simply treated them as 15 isolated research designs that were done on 16 different populations in different places 17 with different considerations. They were not 18 necessarily comparable, like apples to apples 19 or oranges to oranges; they were very 20 different studies in most cases, and so I 21 felt it was important to allow their findings 22 to stand on their own. 23 Q. I want to talk to you about 24 dose-response. That's another of the</p>	<p style="text-align: right;">Page 256</p> <p>1 front of you? 2 A. I do. 3 I would also add that the 4 Penninkilampi meta-analysis also found a 5 dose-response. 6 Q. Do you mention Penninkilampi at 7 all in your report? 8 A. It's cited. 9 Q. In the body of your report? 10 A. I think it's in there 11 somewhere. 12 Q. You believe it is; is that 13 right? 14 A. I do. 15 Q. Well, I'll ask you a couple of 16 questions about it then. 17 Before I do, let's talk a 18 little bit more about your report. So go to 19 page 7. You state at the very top of that 20 page that it has been difficult to estimate 21 dose in order to evaluate the dose-response 22 relationship for ovarian cancer; is that 23 right? 24 A. That's correct.</p>
<p style="text-align: right;">Page 255</p> <p>1 Bradford Hill criteria; is that right? 2 A. That's correct. 3 Q. Which studies show a 4 dose-response, talc exposure and ovarian 5 cancer? 6 A. Let me see here. I'm looking 7 at my notes. The Harlow study from 1992 8 showed a dose-response, and the Cramer 2016 9 study showed a dose trend with strong odds 10 ratios for premenopausal women and hormone 11 therapy-treated women with greater than 12 24 years of exposure. 13 The Schildkraut study, also a 14 case-controlled study of 2016, showed a 15 dose-response. 16 Q. There are a number of studies 17 that did not show a dose-response; is that 18 right? 19 A. It's correct. They did not 20 necessarily show there was not a 21 dose-response. They just, as I was 22 mentioning before, were unable to detect a 23 dose-response. 24 Q. Do you have your report in</p>	<p style="text-align: right;">Page 257</p> <p>1 Q. You state that it also has been 2 difficult to exactly estimate the quantity of 3 talcum powder administration during personal 4 hygiene activities; is that right? 5 A. That's correct. 6 Q. Let's look at a couple of the 7 studies that you believe do, in fact, show a 8 dose-response. The Penninkilampi, that's a 9 meta-analysis, 2018; is that right? 10 A. That's correct. 11 Q. That study does not consider or 12 include the Gertic 2010 cohort study; is that 13 right? 14 A. I -- I'd have to look at the 15 table, but yes, that one may be left out. 16 Q. Well, that's a significant 17 study to leave out of an analysis, isn't it? 18 MS. O'DELL: Object to the 19 form. 20 THE WITNESS: I'm getting 21 there. 22 (Document review.) 23 THE WITNESS: Apologies, I have 24 binder block here.</p>

<p style="text-align: right;">Page 258</p> <p>1 MS. O'DELL: You need help?</p> <p>2 THE WITNESS: Okay.</p> <p>3 BY MR. ZELLERS:</p> <p>4 Q. And I misspoke. I meant to</p> <p>5 refer to Gates, the updated Nurses' study.</p> <p>6 So Gates 2010.</p> <p>7 A. Yes, it appears that Gates is</p> <p>8 not included in the -- in the spectrum of</p> <p>9 studies considering; the Gertic study does</p> <p>10 appear.</p> <p>11 Q. Gates 2010 is an important</p> <p>12 cohort study in this area, would you agree?</p> <p>13 MS. O'DELL: Object to the</p> <p>14 form.</p> <p>15 A. It's important, but I think it</p> <p>16 may be considered one of the ones that</p> <p>17 suffered from power issues. It wasn't able</p> <p>18 to determine a relative risk in the</p> <p>19 population that it assessed.</p> <p>20 BY MR. ZELLERS:</p> <p>21 Q. There are a number of the</p> <p>22 case-control studies that did not determine a</p> <p>23 relative risk, at least of statistical</p> <p>24 significance, correct?</p>	<p style="text-align: right;">Page 260</p> <p>1 Q. This is my highlighted copy, so</p> <p>2 I'm sure it wasn't yours.</p> <p>3 A. I'm sorry.</p> <p>4 Q. That's all right. We'll --</p> <p>5 take your time.</p> <p>6 A. Here we are.</p> <p>7 Q. Got it, Exhibit 20?</p> <p>8 A. I think so.</p> <p>9 Q. Do you have the Cramer study in</p> <p>10 front of you?</p> <p>11 A. I do.</p> <p>12 Q. It's a retrospective</p> <p>13 case-control study published in 2016; is that</p> <p>14 right?</p> <p>15 A. That's correct.</p> <p>16 Q. If we look at the table of</p> <p>17 results on page 337, Table 1.</p> <p>18 Do you see that?</p> <p>19 A. Yes.</p> <p>20 Q. This table shows the risk of</p> <p>21 ovarian cancer for women who use talc, talcum</p> <p>22 powder, daily; is that right?</p> <p>23 MS. O'DELL: Object to the</p> <p>24 form.</p>
<p style="text-align: right;">Page 259</p> <p>1 A. Well, they determined odds</p> <p>2 ratios, which is the equivalent of relative</p> <p>3 risk for a case-control study.</p> <p>4 Q. And in a number of those</p> <p>5 case-control studies, at least 15 out of the</p> <p>6 30 relative risk was not -- or strike that --</p> <p>7 statistical significance was not achieved in</p> <p>8 the study; is that right?</p> <p>9 MS. O'DELL: Object to the</p> <p>10 form.</p> <p>11 A. That's correct.</p> <p>12 BY MR. ZELLERS:</p> <p>13 Q. Let's look at the Cramer paper.</p> <p>14 We've talked about this earlier.</p> <p>15 A. Which one, the 2016?</p> <p>16 Q. Exhibit 20, yes, 2016.</p> <p>17 A. Okay.</p> <p>18 Q. This is another study that you</p> <p>19 cite as being supportive of your</p> <p>20 dose-response opinion; is that right?</p> <p>21 A. Yes.</p> <p>22 Q. Tell me when you have it.</p> <p>23 A. I think you may have picked up</p> <p>24 my copy or the copy that I was looking at.</p>	<p style="text-align: right;">Page 261</p> <p>1 A. It does.</p> <p>2 BY MR. ZELLERS:</p> <p>3 Q. And it's four different periods</p> <p>4 of time; one year, one to five years, five to</p> <p>5 20 years and more than 20 years; is that</p> <p>6 right?</p> <p>7 A. That's correct.</p> <p>8 Q. There was only statistical</p> <p>9 significance found for the time period of one</p> <p>10 to five years of use and more than 20 years</p> <p>11 of use; is that right?</p> <p>12 A. For the first group, the -- for</p> <p>13 those who reported months year of use --</p> <p>14 months per year of use.</p> <p>15 Q. Well, for the first group,</p> <p>16 which was equivalent to one year of daily</p> <p>17 use, there was no statistical significance;</p> <p>18 is that right?</p> <p>19 MS. O'DELL: Object to the</p> <p>20 form.</p> <p>21 A. That -- well, the -- there was</p> <p>22 a positive odds ratio with a nonsignificant</p> <p>23 95% confidence interval.</p> <p>24 ///</p>

<p style="text-align: right;">Page 262</p> <p>1 BY MR. ZELLERS:</p> <p>2 Q. Meaning that if you look at</p> <p>3 this study, that it is certainly possible</p> <p>4 that because there is not statistical</p> <p>5 significance, there could be a finding of no</p> <p>6 risk, correct, no increased risk?</p> <p>7 A. That's a possibility.</p> <p>8 Q. Then if we go to the next</p> <p>9 period, we do show a dose-response for talcum</p> <p>10 powder use in the year -- years one to five;</p> <p>11 is that right?</p> <p>12 A. Well, one to five years of</p> <p>13 daily use, yes.</p> <p>14 Q. But then when we look at five</p> <p>15 to 20 years of daily use, there is not a</p> <p>16 statistically significant association; is</p> <p>17 that right?</p> <p>18 A. That's correct.</p> <p>19 Q. But then when we go to greater</p> <p>20 than 20 years, we do find a statistical</p> <p>21 association; is that right?</p> <p>22 A. That's correct.</p> <p>23 Q. If, in fact, there was a true</p> <p>24 dose-response relationship, you would expect</p>	<p style="text-align: right;">Page 264</p> <p>1 dirty, and it doesn't always work out quite</p> <p>2 that cleanly.</p> <p>3 BY MR. ZELLERS:</p> <p>4 Q. All right. Do you -- well, let</p> <p>5 me withdraw that.</p> <p>6 Confounding. You considered</p> <p>7 and talk about confounding as another one of</p> <p>8 the Bradford Hill criteria; is that right?</p> <p>9 MS. O'DELL: Object to the</p> <p>10 form.</p> <p>11 A. Confounding, by that you mean</p> <p>12 specificity?</p> <p>13 BY MR. ZELLERS:</p> <p>14 Q. Well, I thought your -- I</p> <p>15 thought you said in your methodology that you</p> <p>16 applied the Bradford Hill criteria.</p> <p>17 A. That's correct.</p> <p>18 Q. Is confound -- strike that.</p> <p>19 Is confounding an issue in</p> <p>20 interpreting epidemiologic studies?</p> <p>21 A. Yes.</p> <p>22 Q. Do you agree that there is</p> <p>23 confounding in these studies?</p> <p>24 A. I'm sure there's confounding in</p>
<p style="text-align: right;">Page 263</p> <p>1 to see that dose-response relationship in</p> <p>2 each of these groups; is that right?</p> <p>3 MS. O'DELL: Object to the</p> <p>4 form.</p> <p>5 A. It's more like we see in the</p> <p>6 group directly below that, where you start</p> <p>7 out with an odds ratio which is not</p> <p>8 significant but positive, and then reach a</p> <p>9 significant odds ratio at one to five years</p> <p>10 of daily use and a higher amount of</p> <p>11 significance with five to 20 years of daily</p> <p>12 use, and still a significant odds ratio,</p> <p>13 which is about the same level, at greater</p> <p>14 than 20 years of daily use.</p> <p>15 BY MR. ZELLERS:</p> <p>16 Q. Is that a yes to my question,</p> <p>17 that if you do have a true dose-response</p> <p>18 relationship, you would expect to see that</p> <p>19 dose-response continue throughout each of the</p> <p>20 periods?</p> <p>21 MS. O'DELL: Object to the</p> <p>22 form.</p> <p>23 A. Well, it would be nice if you</p> <p>24 did that, but epidemiologic data is very</p>	<p style="text-align: right;">Page 265</p> <p>1 these studies.</p> <p>2 Q. You're familiar with that term,</p> <p>3 right?</p> <p>4 A. Yes.</p> <p>5 Q. That's where the presence of</p> <p>6 another association confuses the relationship</p> <p>7 between the exposure and the disease being</p> <p>8 studied; is that right?</p> <p>9 A. That's correct.</p> <p>10 Q. For example, if you're studying</p> <p>11 the association between coffee and pancreatic</p> <p>12 cancer, you need to be mindful of whether</p> <p>13 cigarette smoking is more common in coffee</p> <p>14 drinkers than the rest of the population,</p> <p>15 fair?</p> <p>16 A. Yes.</p> <p>17 Q. Coffee -- or strike that.</p> <p>18 Cigarette smoking could be a</p> <p>19 confounder in that situation?</p> <p>20 A. Possible.</p> <p>21 Q. Because if more coffee drinkers</p> <p>22 are smokers than non-coffee drinkers, an</p> <p>23 association between coffee drinking and</p> <p>24 pancreatic cancer might be due to the</p>

<p style="text-align: right;">Page 266</p> <p>1 smoking, not the coffee drinking; fair?</p> <p>2 A. That would be a good</p> <p>3 description of confounding.</p> <p>4 Q. Confounding can distort results</p> <p>5 in epidemiological studies; is that right?</p> <p>6 A. It can.</p> <p>7 Q. Do you agree that residual</p> <p>8 confounding is possible in every</p> <p>9 observational study?</p> <p>10 A. Yes, I think there's some form</p> <p>11 of confounding that's present in every</p> <p>12 observational study.</p> <p>13 Q. It's possible that unmeasured</p> <p>14 confounders may be present in every</p> <p>15 observational study; is that right?</p> <p>16 A. That's correct. Not just</p> <p>17 unmeasured confounders, but unrecognized</p> <p>18 confounders.</p> <p>19 Q. It's impossible to say that all</p> <p>20 known and unknown confounding factors have</p> <p>21 been controlled for in any given study; is</p> <p>22 that right?</p> <p>23 A. I also agree with that.</p> <p>24 Q. Many new factors possibly</p>	<p style="text-align: right;">Page 268</p> <p>1 not controlled for in any of the talc/ovarian</p> <p>2 cancer studies, were they?</p> <p>3 A. Not that I'm aware of.</p> <p>4 Q. Are you aware that studies that</p> <p>5 show a relationship between talc and ovarian</p> <p>6 cancer did not account for confounders?</p> <p>7 A. I think it's possible that many</p> <p>8 of those studies did not account for all</p> <p>9 potential confounders, but they made attempts</p> <p>10 to.</p> <p>11 Q. For example, Terry 2013, we</p> <p>12 talked about that earlier; is that right?</p> <p>13 A. Yes.</p> <p>14 Q. Terry 2013, that meta-analysis</p> <p>15 did not adjust for hormone replacement</p> <p>16 therapy usage, correct?</p> <p>17 A. Yes.</p> <p>18 Q. If hormone replacement therapy</p> <p>19 is a risk factor for ovarian cancer, then the</p> <p>20 Terry 2013 meta-analysis did not account for</p> <p>21 that potential confounding factor, correct?</p> <p>22 MS. O'DELL: Object to the</p> <p>23 form.</p> <p>24 A. Correct.</p>
<p style="text-align: right;">Page 267</p> <p>1 involved in ovarian cancer risk are just</p> <p>2 being published in the literature, correct?</p> <p>3 MS. O'DELL: Object to the</p> <p>4 form.</p> <p>5 A. I believe that is true.</p> <p>6 BY MR. ZELLERS:</p> <p>7 Q. For example, history of</p> <p>8 chlamydia infection, have you read about that</p> <p>9 possibly being involved in ovarian cancer</p> <p>10 risk?</p> <p>11 A. I haven't read that</p> <p>12 specifically. I was thinking more about the</p> <p>13 new information regarding genetic</p> <p>14 susceptibilities.</p> <p>15 Q. Also, weight gain during</p> <p>16 adolescence, is that another relatively new</p> <p>17 possible ovarian cancer risk factor?</p> <p>18 MS. O'DELL: Object to the</p> <p>19 form.</p> <p>20 A. It is, but obesity has been</p> <p>21 recognized as a cofactor for many years.</p> <p>22 BY MR. ZELLERS:</p> <p>23 Q. History of chlamydia infection,</p> <p>24 weight gain during adolescence, those were</p>	<p style="text-align: right;">Page 269</p> <p>1 BY MR. ZELLERS:</p> <p>2 Q. You cannot say whether the odds</p> <p>3 ratio of the Terry 2013 study would have been</p> <p>4 lower if the authors had adjusted for hormone</p> <p>5 replacement therapy usage, correct?</p> <p>6 A. I cannot say that. Yes.</p> <p>7 Q. Recall bias. You're familiar</p> <p>8 with recall bias?</p> <p>9 A. I am.</p> <p>10 Q. That is also a concern in every</p> <p>11 retrospective study, correct?</p> <p>12 A. Yes.</p> <p>13 Q. Recall bias can distort a</p> <p>14 scientific evaluation of whether an exposure</p> <p>15 is actually related to a disease; is that</p> <p>16 right?</p> <p>17 A. Yes, it can.</p> <p>18 Q. For example, recall bias could</p> <p>19 distort results if women with ovarian cancer</p> <p>20 were more likely to remember their exposure</p> <p>21 to talc than women without ovarian cancer; is</p> <p>22 that right?</p> <p>23 MS. O'DELL: Object to the</p> <p>24 form.</p>

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1 A. That's correct.
 2 BY MR. ZELLERS:
 3 Q. The effects of recall bias can
 4 be very real; is that right?
 5 MS. O'DELL: Object to the
 6 form.
 7 A. I'm not sure what you mean by
 8 very real.
 9 BY MR. ZELLERS:
 10 Q. Well, let's look at one of the
 11 studies that you cite. You cited the
 12 Schildkraut study in your report and you
 13 referred to it a bit earlier as supporting
 14 dose-response; is that right?
 15 A. Yes.
 16 Q. That's a study by Schildkraut
 17 and others titled Association Between Body
 18 Powder Use and Ovarian Cancer, the
 19 African-American Cancer Epidemiologic -- or
 20 Epidemiology Study.
 21 Is that right?
 22 A. Yes.
 23 Q. I've got it here for you.
 24 A. Okay.

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1 (Carson Deposition Exhibit 24
 2 marked.)
 3 BY MR. ZELLERS:
 4 Q. Deposition Exhibit 24 is the
 5 Schildkraut study, 2016, correct?
 6 (Pause.)
 7 BY MR. ZELLERS:
 8 Q. Did you say correct?
 9 A. I think I did. I'm sorry.
 10 Q. That's all right. I may have
 11 missed it.
 12 Exhibit 24 is the Schildkraut
 13 2016 study; is that right?
 14 A. Yes.
 15 Q. This is one of the studies that
 16 you cite to and that you relied on in forming
 17 your opinions; is that right?
 18 A. Yes.
 19 Q. The study looked at, among
 20 other things, what impact, if any, lawsuit
 21 filings in 2014 had on whether women recalled
 22 using talc in the past, correct?
 23 A. I believe so.
 24 Q. The authors thought that the

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1 publicity from lawsuits might influence the
 2 participants' recall of prior body powder
 3 use; is that right?
 4 A. This was a recent study, so
 5 that was more likely.
 6 Q. If you look on page 2,
 7 right-hand side, last paragraph that starts
 8 "Covariates include."
 9 Do you see that?
 10 A. Yes.
 11 Q. And I'm reading about
 12 two-thirds of the way down: Two class action
 13 lawsuits were filed in 2014 concerning
 14 possible carcinogenic effects of body powder
 15 which may have influenced recall of use;
 16 therefore, year of interview 2014 or later,
 17 yes/no, was concluded as a covariate in the
 18 logistic regression models.
 19 Is that correct?
 20 A. That's correct.
 21 Q. So go to page 4, Table 2. This
 22 is the adjusted odds ratio for the
 23 associations between mode, frequency and
 24 duration of body powder use in ovarian

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1 cancer; is that right?
 2 A. Yes.
 3 Q. The second column shows the
 4 number of cases, and that would be women with
 5 ovarian cancer; is that right?
 6 A. That's correct.
 7 Q. The third column shows the
 8 controls; that's the women who do not have
 9 ovarian cancer, correct?
 10 A. Yes.
 11 Q. Looking at this data before
 12 2014, before the lawsuits, the percentage of
 13 controls, meaning women without ovarian
 14 cancer, said they used talc on their genitals
 15 was 34%; is that right?
 16 So those are women who were
 17 interviewed before 2014.
 18 A. Yes. Any genital use controls,
 19 34%.
 20 Q. And the controls, again, are
 21 women without ovarian cancer.
 22 A. That's correct.
 23 Q. The percentage of cases,
 24 meaning women with ovarian cancer, that were

<p style="text-align: right;">Page 274</p> <p>1 interviewed before 2014 that said they used 2 talc on their genitals was 36.5%; is that 3 right? 4 A. That's correct. 5 Q. So roughly the same reporting 6 of genital talc use between women with and 7 without ovarian cancer occurred for those 8 women interviewed before the lawsuits were 9 filed; is that right? 10 A. That's correct. 11 Q. Then look at what happened 12 after the lawsuits were filed in 2014. For 13 women interviewed after 2014, the percent of 14 women without ovarian cancer that said they 15 used talc on their genitals was 34.4%; is 16 that right? 17 A. That's correct. 18 Q. So based on this data, the 19 lawsuits had essentially no effect on how 20 many of the women without ovarian cancer, the 21 controls, remembered or recalled using baby 22 powder; is that right? 23 A. Well, the percentage is the 24 same in both cases.</p>	<p style="text-align: right;">Page 276</p> <p>1 BY MR. ZELLERS: 2 Q. In this study, lawsuit filings 3 appears to have affected how many women with 4 ovarian cancer remembered using talc on their 5 genitals but basically had no effect on the 6 memory of women without ovarian cancer; is 7 that right? 8 MS. O'DELL: Object to the 9 form. 10 A. You can't say that this is -- 11 this demonstrates recall bias. It could. 12 BY MR. ZELLERS: 13 Q. These findings could be an 14 example of the potential effect of recall 15 bias; is that right? 16 MS. O'DELL: Object to the 17 form. 18 A. That is correct. 19 BY MR. ZELLERS: 20 Q. So pre-2014 there was an odds 21 ratio of 1.19 with the confidence interval 22 ranging from .87 to -- strike that -- 23 from .87 to 1.63, so there is not statistical 24 significance pre-2014; is that right?</p>
<p style="text-align: right;">Page 275</p> <p>1 Q. It went from 34% to 34.4%; is 2 that right? 3 A. That's correct. 4 Q. For women with ovarian cancer, 5 before the lawsuits were filed, 36.5% of them 6 said they recalled using baby powder; is that 7 right? 8 A. That's right. 9 Q. But after the lawsuits were 10 filed, the percent of women with ovarian 11 cancer who said they used baby powder went up 12 to 51.5%; is that right? 13 A. That is also correct. 14 Q. Is that a significant increase 15 from 36.5%? 16 A. I don't know, but it seems like 17 it might be. 18 Q. So after the lawsuits were 19 filed, the percent of women with ovarian 20 cancer who said they used baby powder jumped 21 significantly; is that right? 22 MS. O'DELL: Object to the 23 form. 24 A. Well, that's -- that is true.</p>	<p style="text-align: right;">Page 277</p> <p>1 A. Probably not. 2 Q. If the study had been 3 terminated as of 2014, prior to the lawsuits 4 being filed, then the results of the study 5 would have been that genital talc use was not 6 statistically significantly associated with 7 an increased risk of ovarian cancer; is that 8 right? 9 MS. O'DELL: Object to the 10 form. 11 A. Yes. 12 BY MR. ZELLERS: 13 Q. Did you make an attempt to 14 account for this potential recall bias in 15 weighing the Schildkraut study? 16 A. The authors did that for me by 17 including the period of the interview as a 18 cofactor in the logistic regression models. 19 It accounts for this difference that you see 20 on the table. 21 Q. You do agree there was no 22 statistically significant finding of an odds 23 ratio prior to 2014, the data collected 24 through that time; is that right?</p>

<p style="text-align: right;">Page 278</p> <p>1 A. In the -- in the data collected 2 on those -- let me see here. In the data 3 collected on those 351 cases and 4 corresponding controls, there was not a 5 significant odds ratio.</p> <p>6 Q. I want to go back and ask you a 7 few questions about some of the things I had 8 talked to you before about.</p> <p>9 In terms of this chatter about 10 IARC, who has told you this?</p> <p>11 A. There are a number of 12 environmental websites and -- that also 13 operate on social media that discuss this 14 kind of thing.</p> <p>15 Q. So there's social media 16 websites that have talked about at least the 17 possibility of IARC revisiting the issue?</p> <p>18 A. Yes, among many other things.</p> <p>19 Q. I asked you earlier about 20 cornstarch, and you believe that cornstarch 21 is rapidly cleared from the body, including 22 the ovaries; is that right?</p> <p>23 MS. O'DELL: Object to the 24 form.</p>	<p style="text-align: right;">Page 280</p> <p>1 factors -- or latency periods for a number of 2 different types of cancers and tumors based 3 on the incidence data and what is known about 4 the natural progression of those tumors over 5 time.</p> <p>6 I can't recall at the moment 7 exactly where I determined the latency period 8 for ovarian cancer to be between 20 and 9 40 years.</p> <p>10 We do have a paper that's 11 referenced here that discusses the 12 determination of latency periods and includes 13 ovarian cancer as one of the tumors that it 14 determines a latency period for, and it uses 15 a mathematical formula with various factors 16 plugged into it to calculate that.</p> <p>17 In that particular article, the 18 latency factor -- period was very long. I 19 think it was 44 years on the average.</p> <p>20 Q. You do not have personal 21 expertise in terms of the latency period for 22 ovarian cancer, correct?</p> <p>23 A. I have -- I've calculated 24 latency periods as an exercise when I was in</p>
<p style="text-align: right;">Page 279</p> <p>1 A. Yes. 2 BY MR. ZELLERS:</p> <p>3 Q. What is the mechanism by which 4 you believe that cornstarch is rapidly 5 cleared from the body, including the ovaries?</p> <p>6 A. It's primarily composed of 7 carbohydrate with a small amount of 8 structural material, probably cellulose, and 9 those materials are broken down in body 10 fluids fairly rapidly and dissolved and 11 become part of the general milieu of the 12 body.</p> <p>13 Q. Does cornstarch create 14 inflammation in the body?</p> <p>15 A. Yes.</p> <p>16 Q. You testified that the latency 17 period for ovarian cancer is between 20 and 18 40 years; is that right?</p> <p>19 A. Roughly, yes.</p> <p>20 Q. What is the basis for you 21 saying that?</p> <p>22 A. There are a number of factors 23 that influence that, but there are 24 organizations that have determined latency</p>	<p style="text-align: right;">Page 281</p> <p>1 graduate school, but that's not something I 2 normally do. I usually defer to the -- those 3 who have published latency periods for that 4 information.</p> <p>5 Q. You are recalling that at least 6 in some of the study or studies that you've 7 reviewed that the latency period for ovarian 8 cancer is 20 to 40 years, correct?</p> <p>9 A. Yes.</p> <p>10 Q. Are you able to tell us which 11 study or studies you're relying on for that 12 information?</p> <p>13 A. I'd have to go through my list 14 to find it. Do you mind if I take a moment 15 to do that?</p> <p>16 Q. Define "a moment."</p> <p>17 A. Well, however long it takes me 18 to find it in that list, but --</p> <p>19 Q. Let me see if I can shortcut 20 it.</p> <p>21 Do you believe that the latency 22 period for ovarian cancer is something you've 23 written out in one of your handwritten notes?</p> <p>24 A. I don't believe so.</p>

<p style="text-align: right;">Page 282</p> <p>1 Q. It would be -- where would it 2 be?</p> <p>3 MS. O'DELL: If you need a 4 moment to review either your report or 5 your materials list, you know --</p> <p>6 THE WITNESS: I don't believe 7 that particular piece of information 8 is in my report, but it's -- I think I 9 could come up with it fairly quickly 10 if I --</p> <p>11 BY MR. ZELLERS:</p> <p>12 Q. All right. Go ahead. Find for 13 us the study or studies you're relying on for 14 the latency period of ovarian cancer.</p> <p>15 A. Okay. If I'm lucky, I may hit 16 on it here.</p> <p>17 (Document review.)</p> <p>18 A. It's the Diana Nadler and Igor 19 Zurbenko paper Estimating Cancer Latency 20 Times Using the Weibull Model.</p> <p>21 BY MR. ZELLERS:</p> <p>22 Q. You're looking at Exhibit 4, 23 your literature list; is that right?</p> <p>24 A. Yes.</p>	<p style="text-align: right;">Page 284</p> <p>1 MS. BOCKUS: If you want to 2 pass me your microphone, I think I can 3 stay here. I'm not going to pass him 4 that many exhibits.</p> <p>5 MR. ZELLERS: I'm happy to help 6 you.</p> <p>7 MS. BOCKUS: Thank you.</p> <p>8 EXAMINATION</p> <p>9 BY MS. BOCKUS:</p> <p>10 Q. Dr. Carson, my name is Jane 11 Bockus. I'm not certain I actually 12 introduced myself to you this morning, but I 13 represent Imerys in this litigation.</p> <p>14 Do you understand that?</p> <p>15 A. I do.</p> <p>16 Q. Before Mr. Abney contacted you 17 about preparing a report that would explain 18 the relationship between regular perineal use 19 of talc based on personal hygiene products 20 and subsequent development of ovarian cancer, 21 is that anything that you had researched 22 before that date?</p> <p>23 MS. O'DELL: Object to the 24 form.</p>
<p style="text-align: right;">Page 283</p> <p>1 Q. What page of Exhibit 4 are you 2 looking at?</p> <p>3 A. Page 17 in the Ns.</p> <p>4 Q. Are you finished?</p> <p>5 A. There may be others in the 6 list, but you asked me to cite one. You want 7 me to continue looking?</p> <p>8 Q. No, I -- that is sufficient for 9 my purposes. Thank you.</p> <p>10 Dr. Carson, there have been 11 some studies where talc particles had been 12 observed or reported in the ovaries of women 13 who have had perineal talc use; is that 14 right?</p> <p>15 A. Yes.</p> <p>16 Q. Heller was one of the studies 17 that we talked about, correct?</p> <p>18 A. Correct.</p> <p>19 Q. In those studies, there has not 20 been inflammation noted; is that right?</p> <p>21 A. No, there -- that's not been an 22 important finding.</p> <p>23 MR. ZELLERS: I have no further 24 questions for you.</p>	<p style="text-align: right;">Page 285</p> <p>1 A. I don't think Mr. Abney -- 2 well, he may have been that detailed in our 3 discussion. But in response to your 4 question, that's not a specific question I 5 had researched in the past, although I had 6 researched related kinds of issues.</p> <p>7 BY MS. BOCKUS:</p> <p>8 Q. So would it be fair to say that 9 the opinions contained in your report are all 10 opinions that you have come to as a result of 11 doing the research at the request of 12 Mr. Abney and others in the plaintiffs' 13 lawyer group?</p> <p>14 MS. O'DELL: Object to the 15 form.</p> <p>16 A. Yes.</p> <p>17 BY MS. BOCKUS:</p> <p>18 Q. Okay. And I'm going to 19 apologize right now. I'll be jumping around 20 because most of my outline has already been 21 covered, so let me just get you to look at 22 your report, if I could, and I'm going to ask 23 you some questions about it.</p> <p>24 Turn to page 4, and</p>

<p style="text-align: right;">Page 286</p> <p>1 paragraph (b), the first sentence reads: 2 Numerous studies have examined the 3 cancer-causing characteristics of talc. 4 Do you see that? 5 A. Yes. 6 Q. And you identified Wilde as 7 your source for that statement, correct? 8 A. That is correct. 9 Q. Isn't it correct that the Wild 10 study actually exonerated talc as having 11 cancer-causing characteristics? 12 A. That was a conclusion of the 13 author, but the reason it's cited there is 14 because that's an example of the 15 investigation of the relationship. 16 Q. Okay. But in that study, 17 they -- he concluded that talc alone did not 18 cause cancer, correct? 19 A. As I recall, that was the 20 general conclusion, yes. 21 Q. Okay. Then in the next couple 22 of sentences, you say that talc has caused 23 cancer when implanted in various tissues and 24 under the skin in laboratory animals. It</p>	<p style="text-align: right;">Page 288</p> <p>1 A. No. 2 Q. And then going on, you talk 3 about the fact that there in that same 4 paragraph, if you go down, you talk about 5 IARC and the fact that IARC concluded that 6 talcum powder use by women for feminine 7 hygiene is a possible human carcinogen; 8 that's not a classification of talc as a 9 carcinogen, correct? 10 MS. O'DELL: Object to the 11 form. 12 A. It is within the spectrum of 13 carcinogens. 14 BY MS. BOCKUS: 15 Q. It's possible. 16 A. That's correct. 17 Q. And then you say that -- 18 meaning that there is insufficient evidence 19 of carcinogenesis in humans, but strong 20 evidence in other mammalian species. 21 Can you tell me where in IARC 22 it says that there is strong evidence that 23 talc causes ovarian cancer in other mammalian 24 species?</p>
<p style="text-align: right;">Page 287</p> <p>1 causes inflammation and fibrotic reaction, 2 including the chemotaxis of inflammatory 3 immune cells and accelerated growth and 4 division of cells in the involved tissue. 5 And you cite Okada 2007 for 6 that proposition; is that correct? 7 A. That's correct. 8 Q. But Okada wasn't even looking 9 at talc, was it? 10 A. Let me see here. Okada was 11 looking at inflammation as -- as the endpoint 12 in the various components of inflammation 13 which I talked about here, the chemotaxis of 14 inflammatory immune cells, accelerated growth 15 division in the involved tissues. 16 Q. But what you say is that talc 17 causes. When you say "it," you're referring 18 to talc, correct? It causes inflammation and 19 fibrotic reaction; isn't that what you're 20 saying in this sentence? 21 A. It is talc, yes. 22 Q. Okay. And yet, Okada, the 23 study that you cite for that proposition, 24 doesn't look at talc at all, does it?</p>	<p style="text-align: right;">Page 289</p> <p>1 A. I think the issue is not 2 specifically ovarian cancer; the issue is 3 cancer. And that's the point of view of 4 IARC, and that's what's alluded to here. 5 Q. So this is the one exhibit I'm 6 going to hand you, if I can get that one 7 marked by my assistant. 8 MR. ZELLERS: Exhibit 25. 9 (Carson Deposition Exhibit 25 10 marked.) 11 MS. O'DELL: This is a page out 12 of the monograph? 13 MS. BOCKUS: Yes. 14 MS. O'DELL: Are you going to 15 identify it? 16 MS. BOCKUS: And he can look it 17 up in his whole monograph. I just 18 pulled the page for simplicity. 19 MS. O'DELL: So feel free to do 20 that, Doctor. 21 MS. BOCKUS: Yes, page 412. 22 BY MS. BOCKUS: 23 Q. So looking at Exhibit 25, this 24 is a page from the IARC monograph where it</p>

<p style="text-align: right;">Page 290</p> <p>1 talks about the data -- the evidence that</p> <p>2 they have and the evidence that they</p> <p>3 reviewed.</p> <p>4 Do you see that?</p> <p>5 A. That's correct.</p> <p>6 Q. And what they actually state</p> <p>7 with regard to experimental evidence is that</p> <p>8 there is limited evidence in experimental</p> <p>9 animals for the carcinogenicity of talc not</p> <p>10 containing asbestos or asbestiform fibers.</p> <p>11 Correct?</p> <p>12 MS. O'DELL: Object to the</p> <p>13 form.</p> <p>14 BY MS. BOCKUS:</p> <p>15 Q. Did I read it incorrectly?</p> <p>16 A. No, I just lost you for a</p> <p>17 moment.</p> <p>18 Q. It's one sentence. Go ahead</p> <p>19 and take your time and read it.</p> <p>20 A. Yes, I agree with that. They</p> <p>21 found that inhaled talc, which does not</p> <p>22 contain asbestos or asbestiform fibers, is</p> <p>23 Group 3.</p> <p>24 Q. That wasn't my question. I'm</p>	<p style="text-align: right;">Page 292</p> <p>1 black, titanium dioxide and talc.</p> <p>2 So regarding talc, the overall</p> <p>3 point of view here is whether or not it</p> <p>4 produces cancer, not just ovarian cancer, not</p> <p>5 just lung cancer, but any cancer.</p> <p>6 And so I'm not sure that that</p> <p>7 responds to your question.</p> <p>8 BY MS. BOCKUS:</p> <p>9 Q. No. My question was: You</p> <p>10 state in your report that IARC found strong</p> <p>11 evidence in animals, and I want to know where</p> <p>12 you believe that statement occurs in the IARC</p> <p>13 monograph, or do you know?</p> <p>14 MS. O'DELL: And if you need a</p> <p>15 minute to look, feel free to do that.</p> <p>16 A. Well, I can say that it might</p> <p>17 take me a while to look for it, but I can say</p> <p>18 that that's the basic definition of Group 2B,</p> <p>19 is limited evidence in humans and compelling</p> <p>20 evidence in animals or other --</p> <p>21 BY MS. BOCKUS:</p> <p>22 Q. Tell me where you're looking at</p> <p>23 that definition of 2B.</p> <p>24 A. Let me see here.</p>
<p style="text-align: right;">Page 291</p> <p>1 talking about experimental animals because</p> <p>2 that's what -- you state in your report that</p> <p>3 IARC found strong evidence in animals, and</p> <p>4 yet the part of IARC that I know of where</p> <p>5 they're addressing the animal data with</p> <p>6 regard to talc is what I handed you in</p> <p>7 Section 6.2, and it states there's limited</p> <p>8 evidence, correct?</p> <p>9 MS. O'DELL: Objection.</p> <p>10 A. It states that there's limited</p> <p>11 evidence -- I need to find this section in</p> <p>12 the monograph. Just bear with me for a</p> <p>13 moment. It's page 412?</p> <p>14 (Document review.)</p> <p>15 A. Okay. I seem to be missing</p> <p>16 that part of the monograph.</p> <p>17 MS. O'DELL: Do you have the 93</p> <p>18 monograph?</p> <p>19 THE WITNESS: Where's the --</p> <p>20 this is 100C, and this is 93. Okay.</p> <p>21 Here it is. All right. Okay.</p> <p>22 A. Okay. The entire monograph is</p> <p>23 designed to evaluate carcinogenic risk, and</p> <p>24 it looks at three different species, carbon</p>	<p style="text-align: right;">Page 293</p> <p>1 Q. We earlier marked the...</p> <p>2 Exhibit 21, I think.</p> <p>3 A. Well, I have this other</p> <p>4 exhibit, which is the preamble from another</p> <p>5 situation; it's Exhibit P-346, and...</p> <p>6 Q. Well, let me just ask a</p> <p>7 different question, rather than looking at</p> <p>8 the preamble.</p> <p>9 A. All right.</p> <p>10 Q. Because that's kind of</p> <p>11 overarching.</p> <p>12 A. It is.</p> <p>13 Q. To know what IARC found with</p> <p>14 regard to talc and the evidence in animal</p> <p>15 models, wouldn't it be more appropriate to</p> <p>16 look at what they actually said about talc in</p> <p>17 the animal studies?</p> <p>18 A. Yes.</p> <p>19 MS. O'DELL: Objection, form.</p> <p>20 A. I would agree that that's the</p> <p>21 case.</p> <p>22 BY MS. BOCKUS:</p> <p>23 Q. And to your knowledge, nowhere</p> <p>24 did they find strong evidence of</p>

<p style="text-align: right;">Page 294</p> <p>1 cancer-causing potential of talc in animal 2 studies, correct?</p> <p>3 MS. O'DELL: Objection to form.</p> <p>4 A. Well -- well, it says on that 5 page there's limited evidence in experimental 6 animals, so I'll agree that at least in this 7 location it does not say strong evidence.</p> <p>8 BY MS. BOCKUS:</p> <p>9 Q. And without going through the 10 entire monograph, you don't know where that 11 language came from, is that fair, that you 12 used in your report?</p> <p>13 MS. O'DELL: Object. Excuse 14 me. Object to the form. I think he 15 was pointing -- directing you to the 16 preamble and you withdrew your 17 question, but --</p> <p>18 MS. BOCKUS: Well, let me just 19 ask a qualifying question.</p> <p>20 BY MS. BOCKUS:</p> <p>21 Q. Does the preamble in any way 22 address their findings with regards to talc?</p> <p>23 A. No, the preamble addresses the 24 methodology that's used by the IARC agency in</p>	<p style="text-align: right;">Page 296</p> <p>1 misstates the evidence.</p> <p>2 A. I believe that was their 3 assumption.</p> <p>4 BY MS. BOCKUS:</p> <p>5 Q. Okay. The studies that you 6 reference in support of the notion that 7 asbestos in -- that may or may not exist in 8 body powder contributes to cause ovarian 9 cancer, none of the studies that you cite to 10 have referenced an application of a product 11 to the perineum of the women and girls study, 12 correct?</p> <p>13 MS. O'DELL: Object to the 14 form.</p> <p>15 THE WITNESS: I have a -- I 16 apologize greatly, but I lost the 17 track. Could you repeat that 18 question.</p> <p>19 MS. BOCKUS: That's totally 20 understandable because it was a little 21 bit convoluted.</p> <p>22 MS. O'DELL: Do you mind if we 23 get the realtime running again? We're 24 just off track here.</p>
<p style="text-align: right;">Page 295</p> <p>1 addressing all the substances that they 2 evaluate.</p> <p>3 Q. Okay.</p> <p>4 A. And that's usually where I pull 5 things like that.</p> <p>6 MS. O'DELL: Are you finished, 7 Doctor?</p> <p>8 THE WITNESS: Unless I'm going 9 to continue to search for this.</p> <p>10 BY MS. BOCKUS:</p> <p>11 Q. I don't need for you to look in 12 the preamble, because I'm really only 13 interested in their findings as to talc, not 14 their overarching methodology, that sort of 15 thing.</p> <p>16 A. Okay. But it's important to 17 point out that this particular monograph is 18 an evaluation of the carcinogenicity of talc 19 that does not contain asbestos or asbestiform 20 fibers, so --</p> <p>21 Q. Correct. Which was, from their 22 view, the talc that was included in all of 23 the studies that they reviewed, correct?</p> <p>24 MS. O'DELL: Objection,</p>	<p style="text-align: right;">Page 297</p> <p>1 MS. BOCKUS: That's okay.</p> <p>2 BY MS. BOCKUS:</p> <p>3 Q. I'm looking on page 5. Do you 4 see on page 5 of your report, sir, 5 paragraph (c)?</p> <p>6 A. Yes.</p> <p>7 Q. And there you cite one, two, 8 three, four, five, six, seven, eight, nine, 9 10, 11, 12 studies, correct?</p> <p>10 A. Yes.</p> <p>11 Q. Do you speak Italian?</p> <p>12 A. I can read it pretty well.</p> <p>13 Q. Is that what you did for the 14 Bertolotti study?</p> <p>15 A. The Bertolotti study. Yes, I 16 read most of it. I may have kibitzed with 17 some of my colleagues about the meaning of a 18 few words.</p> <p>19 Q. At any rate, all of these 20 studies have to do with heavy occupational 21 exposure to asbestos, correct?</p> <p>22 MS. O'DELL: Object to the 23 form.</p> <p>24 A. Yes.</p>

<p style="text-align: right;">Page 298</p> <p>1 BY MS. BOCKUS:</p> <p>2 Q. And you don't have any</p> <p>3 information how the dose of asbestos to which</p> <p>4 these women were exposed during their heavy</p> <p>5 occupational exposure compares to any</p> <p>6 exposure to asbestos from the use of body</p> <p>7 powder, correct?</p> <p>8 A. Well, I think these were not</p> <p>9 all occupational exposures, but I do not have</p> <p>10 information regarding things like the route</p> <p>11 of exposure, no.</p> <p>12 Q. Do you have any information</p> <p>13 regarding the dose?</p> <p>14 A. No, I don't.</p> <p>15 Q. Do you have any information</p> <p>16 that would compare the dose of asbestos to</p> <p>17 which the women in these studies were</p> <p>18 exposed --</p> <p>19 A. Well, in some of the studies --</p> <p>20 Q. Wait, I haven't finished my</p> <p>21 question.</p> <p>22 A. Sorry.</p> <p>23 Q. -- to any alleged dose of</p> <p>24 asbestos in body powder?</p>	<p style="text-align: right;">Page 300</p> <p>1 microenvironment, and based on what we know</p> <p>2 about the mechanism of action of talc as well</p> <p>3 and even asbestos, they're all similar, and</p> <p>4 for that reason would be expected to be</p> <p>5 additive.</p> <p>6 Q. But the study hasn't been done</p> <p>7 even in a petri dish, has it?</p> <p>8 MS. O'DELL: Object to the</p> <p>9 form.</p> <p>10 A. I don't know if there's</p> <p>11 something in progress or not, but that's the</p> <p>12 kind of study that is currently being looked</p> <p>13 at. Combined exposures is the -- sort of the</p> <p>14 hallmark of research these days in</p> <p>15 toxicology.</p> <p>16 BY MS. BOCKUS:</p> <p>17 Q. Do you know of anyone who's</p> <p>18 looking at that question?</p> <p>19 A. I don't.</p> <p>20 Q. Okay. Have any of the heavy</p> <p>21 metals that you have identified been</p> <p>22 identified as carcinogenic to the ovary by</p> <p>23 IARC?</p> <p>24 A. No.</p>
<p style="text-align: right;">Page 299</p> <p>1 Can you make any comparison</p> <p>2 whatsoever to the amount of asbestos to which</p> <p>3 these women were exposed to any exposure by</p> <p>4 any woman who has used a Johnson & Johnson</p> <p>5 body powder?</p> <p>6 MS. O'DELL: Object to the</p> <p>7 form.</p> <p>8 A. I don't think I'm able to make</p> <p>9 that kind of comparison.</p> <p>10 BY MS. BOCKUS:</p> <p>11 Q. Okay. There are ways to study</p> <p>12 whether two toxins combined increase a risk</p> <p>13 more than exposure to a single toxin, whether</p> <p>14 it -- whether one offsets the risk of one of</p> <p>15 the toxins or whether you add them together,</p> <p>16 even multiply them together, right?</p> <p>17 A. Yes.</p> <p>18 Q. Has any such study ever been</p> <p>19 done with regard to talc and the heavy metals</p> <p>20 that you identify in your report?</p> <p>21 A. Not specifically a study to</p> <p>22 look at the combined contribution, but we</p> <p>23 know a lot about the mechanism of action of</p> <p>24 the metals in particular in the</p>	<p style="text-align: right;">Page 301</p> <p>1 Q. I want you to turn to page 7</p> <p>2 now, if you would, please, on other evidence.</p> <p>3 And you've talked about this paragraph a fair</p> <p>4 amount already, and I don't want to repeat</p> <p>5 any of the prior questions.</p> <p>6 But I want to ask you about the</p> <p>7 statement in that first sentence, where you</p> <p>8 say that transport of talc-containing</p> <p>9 materials from the perineum to the upper</p> <p>10 reproductive tract and body cavities has been</p> <p>11 shown to occur with startling regularity.</p> <p>12 And I want to stop right there.</p> <p>13 If I recall your testimony</p> <p>14 correctly, none of these studies even look at</p> <p>15 the transport of talc-containing materials</p> <p>16 from the perineum to the upper reproductive</p> <p>17 tract; isn't that correct?</p> <p>18 MS. O'DELL: Object to the</p> <p>19 form.</p> <p>20 A. Well, it is true that most of</p> <p>21 the research that's been done in this area</p> <p>22 has been done on materials that have been</p> <p>23 instilled into the vagina or the posterior</p> <p>24 fornix, but I think and it's my opinion that</p>

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1 application to the perineum is equivalent to
2 that.

3 Q. Do you have an opinion as to
4 what percentage of the talcum powder applied
5 in a daily dusting to the perineum makes its
6 way to the vagina?

7 A. No, I don't know.

8 Q. Do you have an opinion as to
9 what percentage of the talc that, in your
10 opinion, would make its way to the vagina
11 would actually make its way to the cervix?

12 A. I don't know that either.

13 Q. And out of the talc that makes
14 its way to the cervix, what percentage makes
15 it past the cervix into the uterus?

16 A. That, I don't know either.

17 Q. Do you have any reason to
18 believe that talc would migrate with more
19 frequency or rapidity than sperm?

20 MS. O'DELL: Objection to form.

21 A. No, I don't have reason to
22 believe that would be the case.

23 BY MS. BOCKUS:

24 Q. Would you agree, in fact, that

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1 it is unlikely that talc, an inert particle,
2 would travel as quickly or in the same
3 percentages as sperm through the reproductive
4 tract?

5 MS. O'DELL: Object to the
6 form.

7 A. I think the transport time is
8 roughly the same for any particulate matter,
9 including sperm.

10 BY MS. BOCKUS:

11 Q. Do you have any studies to
12 support that opinion?

13 A. Well, we know -- we know the --
14 we know the velocity of motile sperm; it's
15 very slow. And we have studies that have
16 shown the progression of particles through
17 the fallopian tubes at at least that fast a
18 rate, possibly faster.

19 And so the motility of sperm is
20 slower than the rate at which it passes
21 through the female reproductive system, so
22 there are obviously other mechanisms at play
23 other than sperm motility.

24 Q. To your knowledge, were any of

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1 those studies that you list here done in
2 women who were standing up?

3 A. The studies that I list in
4 other evidence?

5 Q. Yes.

6 A. I think not.

7 Q. In fact, were any of them done
8 in women who were inclined with their head
9 elevated over their hips?

10 A. No.

11 Q. So my question is: Where do
12 you get the term "startling regularity" with
13 regard to the transport of talc from outside
14 a woman's body to the upper reproductive
15 tract?

16 MS. O'DELL: Object to the
17 form.

18 A. The propensity of evidence of
19 rapid transport of particulate material
20 regarding -- regardless of its composition.

21 BY MS. BOCKUS:

22 Q. Particulate material inserted
23 well into a woman's vagina whose hips are
24 above her head, correct?

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1 MS. O'DELL: Objection to form.

2 A. Well, we have other studies
3 too. We have the powdered glove examination
4 studies, things of that nature, that are a
5 little bit different.

6 BY MS. BOCKUS:

7 Q. And you believe they support
8 your conclusion that talc is transported from
9 the perineum to the upper reproductive tract
10 with startling regularity?

11 A. I think that's a valid
12 conclusion supported by the evidence, yes.

13 Q. I'm turning to page 8 now, and
14 the number that you have here -- and you've
15 repeated it a couple of times today -- about
16 your opinion that the elimination of talc as
17 a risk could result in over 3,000 lives saved
18 in the U.S. each year.

19 How did you come to that
20 conclusion?

21 A. Well, I'm referring to talcum
22 powder here --

23 Q. Okay. Sure.

24 A. -- which is the complete

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1 product.

2 I came to that conclusion based
3 on the number of new cases of ovarian cancer
4 that are diagnosed in the United States each
5 year and the number of ovarian cancer deaths
6 that occur each year.

7 And essentially, of 21,000 or
8 so cases of -- new cases of ovarian cancer,
9 there are corresponding 14,000 or more deaths
10 each year, so that's a two-thirds fatality
11 rate if you look over time.

12 The -- at 30% increase in the
13 risk of -- or a 30% increase in the risk of
14 cancer applied in reverse, that is reducing
15 those -- that 30% increased risk from the use
16 of perineal application of talcum powder
17 could result in the prevention of as many as
18 3,000 lives, depending on the prevalence of
19 use.

20 Q. Would that calculation require
21 that 100% of the women in the U.S. be using
22 talcum powder on a daily basis?

23 A. It would require a hundred
24 percent of the women in the U.S. to stop

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1 using talcum powder on a daily basis.

2 Q. That wasn't my question.

3 In order to attribute --

4 A. Well, my answer to your
5 question then is no.

6 Q. In order to attribute 30% of
7 all ovarian cancer deaths to the use of
8 talcum powder -- let me back up.

9 The data that you have that
10 you've cited is talking about the percentage
11 of women -- the percentage of women who use
12 talcum powder who are diagnosed with ovarian
13 cancer, correct?

14 MS. O'DELL: Object to the
15 form.

16 A. It is the total number of new
17 diagnoses per year.

18 BY MS. BOCKUS:

19 Q. Okay.

20 A. I think last year was
21 22,000-something.

22 Q. But that number, 22,000, 100%
23 of those women did not use talcum powder,
24 correct?

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1 A. There may not have been use of
2 talcum powder in all those women, that's
3 correct.

4 Q. Do you have any notion as to
5 what percent of those women may have used
6 talcum powder?

7 A. Based on these various studies,
8 it seems to vary between 30 and 60%. It's
9 more so in the U.S., Australia and the U.K.

10 Q. Do you have an opinion as to
11 how regularly a women needs to use talcum
12 powder before her risk of ovarian cancer is
13 increased by 30%?

14 A. Well, based on the epidemiology
15 studies, that risk occurs in the population
16 in general from ever use as opposed to never
17 use, and so it would depend on the individual
18 woman.

19 Each person has an individual
20 susceptibility and individual characteristics
21 and would probably have an individual use
22 pattern. So I couldn't say for any
23 individual woman.

24 Q. And that's not what I'm asking

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1 for. I'm really asking for in general,
2 because that's what epidemiology is, correct?
3 It's not talking about an individual woman,
4 right?

5 A. That's correct, it's describing
6 it in the population.

7 Q. So in the population, in the
8 studies that you've reviewed, what is the
9 minimum number of days per month, or however
10 you want to describe it, that a woman would
11 need to use talcum powder before she would be
12 included in the group that you believe have a
13 30% increased risk of ovarian cancer?

14 MS. O'DELL: Object to the
15 form.

16 A. The only qualifier that I've
17 been able to come up with and that I've used
18 in this report is the regular use of talcum
19 powder.

20 BY MS. BOCKUS:

21 Q. Okay.

22 A. And that is going to vary over
23 a broad range. It would be periodically
24 daily to several times a week would be

<p style="text-align: right;">Page 310</p> <p>1 regular use.</p> <p>2 Q. And over how many years must a</p> <p>3 woman use talcum powder on a regular basis</p> <p>4 before her risk of ovarian cancer is</p> <p>5 increased to 30% --</p> <p>6 MS. O'DELL: Object to the</p> <p>7 form.</p> <p>8 BY MS. BOCKUS:</p> <p>9 Q. -- in your opinion?</p> <p>10 MS. BOCKUS: Sorry.</p> <p>11 A. Some of the studies have</p> <p>12 focused on usage periods as short as one</p> <p>13 year, but most have studied longer periods of</p> <p>14 use and separated use into things like</p> <p>15 decades or accumulated total person-years</p> <p>16 based on reports of the women, multiplying</p> <p>17 frequency by time.</p> <p>18 So again, it would depend on</p> <p>19 the individual, but the research reports</p> <p>20 hover around five to ten years of regular</p> <p>21 use, resulting in significant odds ratios.</p> <p>22 BY MS. BOCKUS:</p> <p>23 Q. As I understand it in</p> <p>24 toxicology, one of the basic tenets is that</p>	<p style="text-align: right;">Page 312</p> <p>1 no threshold of exposure for risk; that we</p> <p>2 are -- we are right to use a zero threshold</p> <p>3 approach until we know more about the</p> <p>4 possibility of a threshold below which</p> <p>5 exposure would be safe. At the current time</p> <p>6 we don't have that information.</p> <p>7 Q. Do you believe that there</p> <p>8 probably is a threshold below which use is</p> <p>9 safe?</p> <p>10 A. In the carcinogenic process,</p> <p>11 which we haven't really talked about in this</p> <p>12 session today, there is an insult to a cell</p> <p>13 which affects the genetic material, the DNA.</p> <p>14 And there are built-in repair mechanisms that</p> <p>15 the cell has for fixing that problem that</p> <p>16 occurred, a mutation, for example.</p> <p>17 These kinds of insults are</p> <p>18 happening to cells all the time, not just</p> <p>19 from carcinogens in our environment, but just</p> <p>20 from natural occurrences, even endogenous</p> <p>21 biochemical reactions cause these problems.</p> <p>22 The question is: Is the repair</p> <p>23 process sufficient to undo what's been done?</p> <p>24 And an exposure to environmental carcinogens,</p>
<p style="text-align: right;">Page 311</p> <p>1 it's the dose that makes the poison, correct?</p> <p>2 A. That's correct.</p> <p>3 Q. That water can kill you if you</p> <p>4 drink too much of it, right?</p> <p>5 A. Theoretically.</p> <p>6 Q. In a short period of time.</p> <p>7 And so I'm trying to find out</p> <p>8 what you have determined is the threshold of</p> <p>9 risk is -- for talcum powder use by women.</p> <p>10 Do you have an opinion as to at what point a</p> <p>11 threshold has been reached where the use of</p> <p>12 talcum powder by women in their perineal</p> <p>13 region increases their risk?</p> <p>14 A. I think any use of carcinogenic</p> <p>15 materials or any exposure to carcinogenic</p> <p>16 materials increases the risk somewhat. A</p> <p>17 greater exposure, based on the</p> <p>18 "dose makes the poison" principle, would</p> <p>19 result in a greater risk.</p> <p>20 And we know from toxicologic</p> <p>21 studies that intense exposures can sometimes</p> <p>22 accelerate the process and even shorten the</p> <p>23 latency period of a carcinogenic event.</p> <p>24 So my opinion is that there is</p>	<p style="text-align: right;">Page 313</p> <p>1 that repair process is often overwhelmed so</p> <p>2 that it cannot catch up with the damage</p> <p>3 that's being created, and a tumor is born,</p> <p>4 basically.</p> <p>5 That is where the concept of</p> <p>6 threshold comes from. Have we overwhelmed</p> <p>7 the repair or not, and we don't have enough</p> <p>8 research evidence or scientific evidence to</p> <p>9 be able to define that line at this point.</p> <p>10 Q. Has there ever been a study</p> <p>11 that showed that talcum powder caused DNA</p> <p>12 damage in normal ovarian epithelial tissue?</p> <p>13 A. Well, we do have the studies</p> <p>14 that have recently been produced by Fletcher</p> <p>15 and Saed that show the inflammatory process</p> <p>16 is influenced by talc, and this is nonfibrous</p> <p>17 talc, that result in mutagenic events that</p> <p>18 are available for promotion, and there are</p> <p>19 biomarkers that have also been established</p> <p>20 for that.</p> <p>21 Q. The studies by Saed did not</p> <p>22 demonstrate DNA mutation, did they?</p> <p>23 MS. O'DELL: Object to the</p> <p>24 form.</p>

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1 A. I think they actually did.
 2 BY MS. BOCKUS:
 3 Q. That's your reading of them?
 4 A. Yes.
 5 Q. What Saed did is he placed talc
 6 on cultured ovarian cancer cells, correct?
 7 A. Yes.
 8 Q. And that actually -- what he
 9 recorded was an elevation in the CA-125?
 10 A. That's one of the things he
 11 did. He also measured -- he did a number of
 12 genetic studies. He did transcribed RNA. He
 13 located individual SNPs, which are single
 14 nucleotide polymorphisms, in the genetic
 15 material.
 16 And he found that as a result
 17 of that treatment, those mutations altered
 18 the effectiveness of antioxidant enzymes that
 19 are part of the protection mechanism and
 20 shield the repair process of the cell from
 21 further damage.
 22 Q. Let's go back to the CA-125.
 23 MS. O'DELL: If you need to
 24 pull the paper out, Doctor, just, if

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1 you want to take a moment and do that.
 2 I know you were searching for it while
 3 you were talking.
 4 THE WITNESS: Yes, I think I
 5 have it right here.
 6 MS. BOCKUS: These are just
 7 general questions that I'm going to
 8 ask you.
 9 MS. O'DELL: You still may get
 10 the paper out.
 11 MS. BOCKUS: Do whatever you
 12 want to do.
 13 THE WITNESS: You can go ahead.
 14 I'm...
 15 BY MS. BOCKUS:
 16 Q. What controls did Saed use?
 17 Did he use any controls? In other words, did
 18 he place a known foreign object that was
 19 not -- that was known not to be a carcinogen
 20 on the cultured ovarian cells to see if there
 21 was a difference?
 22 MS. O'DELL: Can you just pause
 23 just for a minute, let the doctor pull
 24 out the exhibit?

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1 THE WITNESS: I'm sorry, it
 2 appears that I do need to get the
 3 original paper here. There it is.
 4 Okay. Thank you.
 5 (Document review.)
 6 BY MS. BOCKUS:
 7 Q. Can you answer the question:
 8 Did Saed have any either positive or negative
 9 controls that he used in his experiments?
 10 MS. O'DELL: Object to the
 11 form.
 12 A. I think he did, but I'd like to
 13 actually find it in here so I can give you
 14 the specifics.
 15 Well, he used normal cells and
 16 epithelial ovarian cancer cells, and one was
 17 the control for the other. He treated them
 18 in the same way.
 19 BY MS. BOCKUS:
 20 Q. Let me ask a different
 21 question.
 22 What I'm asking is: Did he
 23 use, say, glass beads to see if -- as a
 24 control to the talc? Did he have anything

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1 that he was controlling the cells' reaction
 2 to against the talc?
 3 A. I don't believe so.
 4 Q. That would be important in an
 5 experiment of this nature, would you not
 6 agree with that?
 7 MS. O'DELL: Object to the
 8 form.
 9 A. Well, he did utilize normal and
 10 cancerous cells, which would theoretically
 11 act as a control in that experiment.
 12 BY MS. BOCKUS:
 13 Q. That's not my question. I'm
 14 really asking about another element that he
 15 is exposing the cells to, both the normal and
 16 the cancerous cells.
 17 MS. O'DELL: Objection to form.
 18 BY MS. BOCKUS:
 19 Q. To see if the reaction was just
 20 a reaction to a foreign body versus talc
 21 specifically.
 22 Did he do that?
 23 MS. O'DELL: Object to the
 24 form.

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1 A. I don't believe that he
2 provided a control exposure as part of this
3 experiment.
4 BY MS. BOCKUS:
5 Q. And you would agree that there
6 are many things that will increase a CA-125,
7 correct?
8 MS. O'DELL: Object to the
9 form.
10 A. Yes, it's an acute-phase
11 reactant.
12 BY MS. BOCKUS:
13 Q. Pregnancy can increase
14 somebody's CA-125?
15 A. That's correct.
16 Q. And with regard to the SNPs,
17 that is not the same thing as a test showing
18 mutation, correct?
19 MS. O'DELL: Object to the
20 form.
21 BY MS. BOCKUS:
22 Q. It's a surrogate.
23 A. Well, it's because there was
24 transcribed RNA that was used to determine

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1 their presence, and the -- it's just part of
2 their procedure, but it identifies genetic
3 alterations. And those genetic alterations
4 transformed into differential enzyme
5 activities.
6 Q. Do you know whether there are
7 standard tests for genotoxicity and
8 mutagenicity?
9 A. There are lots of standard
10 tests, yes.
11 Q. And Saed didn't use any of
12 those, did he?
13 MS. O'DELL: Object to the
14 form.
15 A. Well, he went directly to cells
16 in culture to see what happened when they
17 were treated with talc.
18 BY MS. BOCKUS:
19 Q. Does the amount of talc that
20 Saed used compare in any way to the amount of
21 talc that may reach a woman's ovary from
22 perineal application?
23 MS. O'DELL: Object to the
24 form.

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1 A. I don't specifically know.
2 BY MS. BOCKUS:
3 Q. There's no way to know that, is
4 there?
5 A. No, there's not.
6 Q. Let me find my -- there we go.
7 The Saed paper that you were
8 looking at just a minute ago, it has
9 something printed across it. What does that
10 say?
11 A. In blue here?
12 Q. Uh-huh.
13 A. "For Peer Review."
14 Q. Okay. So it hasn't yet been
15 peer reviewed; is that correct?
16 MS. O'DELL: Object to the
17 form.
18 A. It's been submitted.
19 BY MS. BOCKUS:
20 Q. So does that mean it has not
21 yet been peer reviewed?
22 MS. O'DELL: Object to the
23 form.
24 A. I think it's been accepted for

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1 publication.
2 BY MS. BOCKUS:
3 Q. But the copy you have says on
4 it "For Peer Review," correct?
5 A. That's correct.
6 Q. In the paragraph that we were
7 looking at earlier, where you were talking
8 about the startling regularity, later on in
9 the paragraph you state that there
10 is clearly -- sufficient particulate
11 materials applied routinely to the perineum
12 have ready access and in sufficient
13 quantities to produce biologic responses in
14 internal tissues.
15 What internal tissues have you
16 seen any study recording a biologic response
17 to talc from?
18 That was such a bad question,
19 I'm going to ask it again.
20 What internal tissues are you
21 referring to there?
22 A. Well, it says including --
23 including ovaries and surrounding structures.
24 By surrounding structures, I'm referring to

<p style="text-align: right;">Page 322</p> <p>1 the fallopian fimbriae and the epithelium of 2 the cavity. 3 Q. So -- and I know we've been 4 through this already, but to your knowledge, 5 there are no studies reporting biologic 6 responses to talc in the vagina, correct? 7 A. Not that I'm aware. 8 Q. You're not aware of any studies 9 reporting biologic responses to talc in the 10 cervix, correct? 11 A. Correct. 12 Q. Are you aware of any studies 13 reporting biologic response to the uterus? 14 A. No. 15 Q. Are you aware of any studies 16 reporting a biologic response in the 17 fallopian tubes? 18 MS. O'DELL: Object to the 19 form. 20 A. Well, I don't -- I'm not aware 21 of studies that draws a direct correlation 22 between exposure to talc and reaction in the 23 fallopian tubes. 24 ///</p>	<p style="text-align: right;">Page 324</p> <p>1 fallopian tube goes into that fluid and just 2 gets moved around all the time; is that 3 correct? 4 MS. O'DELL: Objection. Excuse 5 me. Objection, form. 6 A. Well, there's a fairly direct 7 presentation of the ovary, so there's not a 8 large space there, but there is a space. And 9 whatever goes into that space remains there. 10 Some of it may come back out. 11 BY MS. BOCKUS: 12 Q. Does the fallopian tube move 13 around during the month? 14 MS. O'DELL: Object to the 15 form. 16 A. I don't know. 17 MS. BOCKUS: I'm almost 18 finished. I'm going through all the 19 things that I've crossed off. 20 BY MS. BOCKUS: 21 Q. So I understand you correctly, 22 you have not identified a nonthreshold dose 23 of talc; is that correct? 24 MS. O'DELL: Object to the</p>
<p style="text-align: right;">Page 323</p> <p>1 BY MS. BOCKUS: 2 Q. Okay. Is the ovary attached to 3 the fallopian tube? 4 A. It is -- it's in the proximity. 5 It's not directly attached. 6 Q. And what surrounds the ovary? 7 A. There's a structure that -- the 8 ovary itself? 9 Q. Yes. 10 A. There's an epithelial membrane 11 around the ovary, and -- 12 Q. And then what touches the 13 epithelial membrane? 14 A. Well, the fimbriae of the 15 fallopian tubes surround that and the rest of 16 it is just sort of space. 17 Q. Space. Is the space filled 18 with fluid? 19 A. It is. 20 Q. And is that fluid kind of 21 moving around? 22 A. All the time. 23 Q. All the time. 24 So things that come through the</p>	<p style="text-align: right;">Page 325</p> <p>1 form. 2 A. You mean a dose that is below a 3 safe threshold? 4 BY MS. BOCKUS: 5 Q. Correct. 6 A. No, I have not. 7 Q. Did you make any attempt to 8 extrapolate a de minimis risk level? 9 MS. O'DELL: Object to the 10 form. 11 A. I did not. It would be nice to 12 be able to do that, considering that most of 13 us have had talcum powder exposures of one 14 sort or another during our lives. And it's 15 something that seems to have been felt to be 16 very useful. 17 So it would be nice to be able 18 to do that exercise, but I haven't -- I have 19 not been prevented -- presented with the 20 information to approach that, nor am I aware 21 of anyone else who's been able to do it. 22 BY MS. BOCKUS: 23 Q. What information would you need 24 that you don't have?</p>

<p style="text-align: right;">Page 326</p> <p>1 A. Well, we'd need -- we'd need 2 dose information, first of all, which we 3 don't have, to combine with the epidemiologic 4 results. 5 We need to define the 6 mechanistic issues better than they are 7 currently, and at that point I think we would 8 be able to make some strong conclusions 9 regarding potential thresholds of hazardous 10 doses. 11 Q. You would agree that the great 12 majority of women who use talcum powder on a 13 regular basis are never diagnosed with 14 ovarian cancer, correct? 15 A. I think that's true. 16 Q. And it's also true that the 17 majority of women diagnosed with ovarian 18 cancer have never used talcum powder on a 19 regular basis, correct? 20 MS. O'DELL: Object to the 21 form. 22 A. I think it's a majority, but 23 there's a significant number who have. 24 ///</p>	<p style="text-align: right;">Page 328</p> <p>1 you? In other words, are they referred by 2 other people? 3 A. I have primarily a referral 4 practice in toxicology. 5 Q. In toxicology? And so what 6 types of patients are referred to you? 7 A. I have patients who are either 8 workplace-related patients who have had 9 chemical or other substance exposures. I 10 also have a number of environmental exposure 11 patients that I see. 12 And I also have a number of -- 13 I also see a number of patients for general 14 routine surveillance activities or required 15 exams by regulation, either for licensure or 16 certification. 17 Q. Are you sent patients where the 18 patient is trying to figure out why they got 19 some disease? 20 A. Sometimes. Usually the patient 21 comes and tells me why they got the disease, 22 and I go -- I talk to them about the 23 possibilities, and we look at ways of 24 confirming that or refuting it, or in many</p>
<p style="text-align: right;">Page 327</p> <p>1 BY MS. BOCKUS: 2 Q. But the majority have not, 3 correct? 4 A. I would say more than 50% have 5 not. 6 Q. And would you agree that -- let 7 me back up. 8 When is the last time you 9 conducted a pelvic exam? 10 A. I haven't done one in a couple 11 of years. 12 Q. Under what circumstances did 13 you do it two years ago? 14 A. I see patients regularly, and 15 in some cases, pelvic exams are either 16 requested or indicated by the issue. 17 Q. It's not something you do on a 18 regular basis, correct? 19 A. It's not. 20 Q. And you do not -- what 21 percentage of your patients are women? 22 A. Probably half, maybe a little 23 less than half. 24 Q. How do patients come to see</p>	<p style="text-align: right;">Page 329</p> <p>1 cases, altering to a correct path of 2 diagnostic investigation. 3 Q. So sometimes a patient comes to 4 you and says: I was exposed to this chemical 5 and that's why I can't breathe? 6 A. Yes. 7 Q. And you do an investigation, 8 and sometimes you say: You know what, that 9 chemical has nothing to do with why you can't 10 breathe? 11 A. Sometimes that's the case. 12 MS. O'DELL: Are you finished, 13 sir? Are you finished? 14 A. Well, I just wanted to add -- 15 BY MS. BOCKUS: 16 Q. Sure. 17 A. -- that although many times it 18 is the case, and often the patient does 19 understand that connection quite well, 20 usually from a very closely connected cause 21 and effect kind of relationship. It's when 22 things are stretched out much more in time, 23 and there is a likely suspect that may be an 24 innocent bystander, that they may get</p>

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1 confused.

2 Q. Have you ever been referred a
3 patient to determine why they have ovarian
4 cancer?

5 A. No.

6 Q. Do you know of any methodology
7 accepted in the medical community for
8 determining why an individual woman has
9 developed ovarian cancer?

10 MS. O'DELL: Object to the
11 form.

12 A. Other than genetic testing that
13 identifies specific risks and history taking
14 that might identify other known risk factors
15 for that woman, there is -- I don't believe
16 that there is any good or prescribed
17 procedure for making that determination, and
18 there is no reasonable screening test that
19 can find that cancer when it is at an early
20 stage.

21 BY MS. BOCKUS:

22 Q. Do you believe that obesity
23 causes ovarian cancer?

24 A. It certainly seems to be

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1 related to the occurrence of ovarian cancer
2 from a statistical point of view.

3 Q. What is the increase in a
4 woman's risk of ovarian cancer if she's obese
5 compared to a nonobese woman?

6 A. In terms of numbers?

7 Q. Yes, sir.

8 A. I don't know the -- I don't
9 know the numbers.

10 Q. What other risk factors are you
11 familiar with for ovarian cancer?

12 A. Well, certainly work with
13 asbestos is a risk factor, and we have a
14 number of studies that have shown women
15 working in the asbestos industry or women who
16 are married to asbestos workers and have
17 secondary exposure presumably from that are
18 at risk for ovarian cancer.

19 There are --

20 Q. Let me stop you just one
21 second.

22 A. Yes.

23 Q. What percentage -- what is
24 their relative risk or what is the odds ratio

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1 for that population of women?

2 A. Well, it varies depending on
3 the research study that has been done, but
4 I've seen odds ratios or relative risks all
5 the way from 1 or even below to very high
6 numbers, like 20 to 50.

7 Q. 20.0, is that what you're
8 saying?

9 A. Yes, 20.0.

10 Q. Not 1.2, but 20.0?

11 A. Correct.

12 Q. Okay.

13 A. Which is a -- which would be 20
14 times the normal risk without the exposure.

15 Q. Okay. So we've got obesity and
16 heavy exposure to asbestos. Any other risk
17 factors that you're familiar with?

18 MS. O'DELL: Objection --
19 excuse me. Objection, misstates the
20 doctor's testimony.

21 You may answer.

22 THE WITNESS: Okay.

23 A. Other risk factors for ovarian
24 cancer would include things like early

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1 menarche, late menopause, never being
2 pregnant. These are some of the more common
3 risk factors that are identified.

4 There are genetic risk factors
5 that are known, like the BRCA mutations,
6 which confer an increased risk. Family
7 history.

8 BY MS. BOCKUS:

9 Q. Do you know the odds ratios of
10 any of the risk factors that you just
11 identified of never having children, having
12 early menarche or late menopause?

13 A. Right offhand, I don't know
14 what those odds ratios -- the range of those
15 are.

16 Q. Do you know if any of those
17 odds ratios exceed 1.3?

18 A. I think they do.

19 Q. Does that lead you to conclude
20 that those things cause ovarian cancer?

21 A. It certainly argues for that.
22 The -- there's a risk factor that derives
23 from something. You need a mechanism to fill
24 in the blank.

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1 But also, some of these risk
 2 factors are so common in the population that
 3 we can concoct large cohort studies that will
 4 have -- can have very low relative risks,
 5 like on the order of 1.3 or even lower, and
 6 still a significant result.

7 So the more common a factor is,
 8 the easier it is to do the research and the
 9 more likely you'll get a finding that's
 10 relevant to interpretation.

11 Q. What pushes a talc particle
 12 from the perineum into the vagina?

13 A. Probably mostly the law of mass
 14 action. It simply goes of its own volition.
 15 These small particles are always in motion
 16 through molecular forces, and they simply
 17 move in all directions, and some of them move
 18 in that direction.

19 Q. Would that be true for any
 20 small particles applied to a woman's
 21 perineum?

22 A. Yes.

23 Q. Are you board certified in
 24 medical toxicology?

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1 A. I'm not. I started practicing
 2 medical toxicology before there was a board
 3 in the specialty, and I've been grandfathered
 4 into the profession as a member of the
 5 American College of Medical Toxicology.

6 Q. How long did you talk to
 7 Dr. Ness about her paper?

8 A. About her paper, probably a
 9 minute and a half. About all kinds of other
 10 things, for a while.

11 Q. What other kinds of things?

12 A. Mostly personal things that had
 13 nothing to do with talc or this case.

14 Q. How long do you think that
 15 conversation was?

16 A. Well, with Dr. Ness, nothing
 17 lasts very long, so I would say ten minutes
 18 at the most.

19 Q. Okay. Did you call her?

20 A. No. She's -- she comes and
 21 goes in the same building where I office, and
 22 my office is just on the opposite side of the
 23 floor of hers, and I see her sometimes in
 24 passing or in the elevator.

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1 Q. So you think you just ran into
 2 her?

3 A. Yeah.

4 Q. The other people that you
 5 identified that you discussed your report
 6 with, did you ask them to read your report?

7 A. I asked them to look at parts
 8 of it, early drafts of it to let me know if
 9 they thought I was making sense.

10 Q. And did they offer you comments
 11 and suggestions for changes in your paper?

12 A. Not really. Mostly they gave
 13 me a pat on the back and said: I think
 14 you're doing a good job, just sort of beef
 15 this part up, and what do you mean by this,
 16 maybe I could rephrase that. That sort of
 17 thing.

18 Q. Did they give you written
 19 suggestions?

20 A. No, these were all verbal
 21 comments.

22 Q. Had you given them a hard copy
 23 of the portions of your report that you
 24 wanted them to comment on?

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1 A. Yes.

2 Q. And they didn't redline it or
 3 make -- draw arrows or anything like that for
 4 you?

5 A. I think actually George Delclos
 6 did draw some -- or make some notes on there
 7 and hand it back to me, and I incorporated
 8 those into my electronic version.

9 Q. Do you still have George's
 10 notes to you?

11 A. No, I don't.

12 Q. Is he the only one out of the
 13 people that you asked to look at it who gave
 14 you handwritten notes?

15 A. Yes, I think so.

16 Q. Have you seen the term
 17 "intrinsic elimination system" regarding the
 18 ovary in any of the publications that you've
 19 read?

20 A. I don't know, I may have.

21 Q. Can you think of one in
 22 particular that discusses that characteristic
 23 of -- that you believe relates to the ovary?

24 A. Well, the migration papers

<p style="text-align: right;">Page 338</p> <p>1 discuss migration to the ovary. It would 2 probably be a talc paper, though. I don't 3 recall seeing it anywhere. 4 Q. Did you consult any gynecologic 5 textbooks? 6 A. No, I didn't. I may have 7 looked at some diagrams on the Internet. 8 Q. Okay. Did you consult any 9 gynecologic oncology textbooks? 10 A. Not textbooks, no. 11 Q. Do you know the position of the 12 Society of Gynecologic Oncologists on the 13 question of whether does talc increase a 14 woman's risk for ovarian cancer? 15 A. No, I don't. 16 Q. Would that be important to you 17 to know their position? 18 A. No, I don't think so. 19 Q. Do you know the position of 20 ACOG on whether the use of -- perineal use of 21 talc increases a woman's risk of ovarian 22 cancer? 23 A. I don't know that either. 24 That's not something I've looked at.</p>	<p style="text-align: right;">Page 340</p> <p>1 that? 2 A. Well, I saw this actually when 3 I first started this process, and I think 4 Dr. Longo was involved in that activity, 5 where they modeled the -- the application of 6 talcum powder and did some calculations based 7 on the amount of substance that was used, and 8 they measured it in things like shakes and -- 9 and then quantified the amount that was lost 10 from the container to determine what an 11 application amount was. 12 I don't think they were able to 13 go beyond that point in the modeling process. 14 Q. You didn't see anything that 15 Dr. Longo did that attempted to quantify the 16 amount of talcum powder from a single shake 17 that ended up on a woman's perineum, did you? 18 MS. O'DELL: Object to the 19 form. 20 A. I -- you know, I don't know the 21 answer to that, simply because I don't 22 recall, but I wouldn't be surprised that 23 there was an attempt made to do that. But 24 beyond that, I don't think anything would be</p>
<p style="text-align: right;">Page 339</p> <p>1 Q. Would that be important to you? 2 A. No. 3 Q. Do you have any scientific text 4 that suggests that an inert particle resides 5 on the ovary longer than it does in the 6 cervix? 7 A. Well, I have -- I have a paper 8 that relates to the time for dissolution of a 9 particle in biological fluids, which would go 10 to the length of time a particle of talc 11 remains in the ovary once it gets there. 12 But I don't have -- I don't 13 know that I have a scientific paper that 14 specifically says that it stays in the ovary 15 longer than it stays in the cervix. 16 Q. You testified that you 17 understand there have been some attempts to 18 quantify the amount of talc, I guess from a 19 single use, that ends up on the perineum. 20 Did I understand that 21 correctly? 22 A. Yes. 23 Q. Can you tell me what those 24 attempts are, who did them, where did you see</p>	<p style="text-align: right;">Page 341</p> <p>1 successful. 2 These were clothed subjects, so 3 that adds another factor to the calculation. 4 BY MS. BOCKUS: 5 Q. Is that the only experiment 6 that you're familiar with that you've seen 7 anywhere that attempts to quantify the amount 8 of talcum powder from a single use that ends 9 up actually on a woman's perineum? 10 A. There was another part of that 11 study where they applied it to underwear with 12 the same sort of calculation process. It was 13 all part of the same modeling process. 14 Q. And do you recall what 15 percentage of the talc applied to the 16 underwear ended up adhered to the woman's 17 perineum? 18 MS. O'DELL: Object to the 19 form. 20 A. I don't think -- I don't think 21 they measured the amount that adhered to the 22 perineum. I think what they were interested 23 in was proximity. 24 ///</p>

<p style="text-align: right;">Page 342</p> <p>1 BY MS. BOCKUS:</p> <p>2 Q. Okay. Can you tell me the</p> <p>3 names of the environmental websites that have</p> <p>4 been talking about IARC revisiting their</p> <p>5 classification of talc?</p> <p>6 A. There are -- there are a number</p> <p>7 of Twitter feeds and websites that carry on</p> <p>8 this kind of discussion. Science Interest is</p> <p>9 one of them. I think IARC Watch is another</p> <p>10 one. I have -- I get e-mails about some of</p> <p>11 these and end up going into them for a period</p> <p>12 of time and seeing if they have anything</p> <p>13 interesting going on. Some of them are</p> <p>14 searchable.</p> <p>15 And then I get e-mails from the</p> <p>16 ones that I visit about other ones. So I</p> <p>17 spend as much of my time deleting these</p> <p>18 e-mails without reading them as I do actually</p> <p>19 viewing the material.</p> <p>20 Q. So fair to say this is just</p> <p>21 chatter you've seen on the Internet in these</p> <p>22 different chat rooms or Twitter accounts that</p> <p>23 you visit from time to time?</p> <p>24 A. It's all Internet based, yes.</p>	<p style="text-align: right;">Page 344</p> <p>1 A. Uh-huh.</p> <p>2 Q. And echoing what my colleagues</p> <p>3 have said today, if there's at any point I</p> <p>4 ask a question that you do not understand,</p> <p>5 just stop me and ask me to rephrase it or let</p> <p>6 me know otherwise, okay?</p> <p>7 A. I will.</p> <p>8 Q. Thanks.</p> <p>9 So going back shortly to your</p> <p>10 scope of work, do you teach any coursework on</p> <p>11 talc or ovarian cancer?</p> <p>12 A. I teach some general courses.</p> <p>13 Up until last spring I taught a general</p> <p>14 environmental health course for graduate</p> <p>15 students in the Master of Public Health</p> <p>16 program at the School of Public Health, and</p> <p>17 in that course we did touch on things like</p> <p>18 environmental exposures that would include</p> <p>19 minerals of various varieties, but it was</p> <p>20 very cursory.</p> <p>21 Q. And was that curriculum</p> <p>22 specific to environmental and industrial</p> <p>23 products or minerals as opposed to consumer</p> <p>24 products?</p>
<p style="text-align: right;">Page 343</p> <p>1 MS. BOCKUS: Okay. I think</p> <p>2 that's all I have. Thank you.</p> <p>3 MS. O'DELL: Why don't we take</p> <p>4 a short break. We've been going about</p> <p>5 two hours.</p> <p>6 MR. ZELLERS: Do you have</p> <p>7 questions?</p> <p>8 MS. APPEL: I do, but --</p> <p>9 MS. O'DELL: Yeah, do you</p> <p>10 have --</p> <p>11 MS. APPEL: I don't have a lot.</p> <p>12 MS. O'DELL: Okay. Sure. Why</p> <p>13 don't you go ahead, and then we'll</p> <p>14 take a break. We have been going</p> <p>15 about two hours, but, Renée, please.</p> <p>16 If you're okay, Doctor.</p> <p>17 THE WITNESS: I'm fine.</p> <p>18 EXAMINATION</p> <p>19 BY MS. APPEL:</p> <p>20 Q. It's been a while since we did</p> <p>21 introductions, so just as a reminder, my name</p> <p>22 is Renée Appel and I'm here on behalf of</p> <p>23 Seyfarth Shaw and I represent Personal Care</p> <p>24 Products, counsel.</p>	<p style="text-align: right;">Page 345</p> <p>1 A. We actually did touch on other</p> <p>2 consumer products as well in terms of the</p> <p>3 significant environmental problem that we</p> <p>4 have currently, but -- regarding the huge</p> <p>5 volume of personal care products that goes</p> <p>6 into our aqueous waste stream and how that's</p> <p>7 affecting the aquatic environment as well as</p> <p>8 groundwater and so forth.</p> <p>9 As a matter of fact, in that</p> <p>10 course, as part of the culmination of the</p> <p>11 course, there are student workgroups that</p> <p>12 develop presentations on a particular topic,</p> <p>13 and the topic of personal care products has</p> <p>14 been a favorite choice for the last several</p> <p>15 years.</p> <p>16 Q. But your curriculum did not</p> <p>17 include talc among those products?</p> <p>18 MS. O'DELL: Object to the</p> <p>19 form.</p> <p>20 A. I think talc may have been</p> <p>21 represented as an individual mineral on a</p> <p>22 slide that listed many minerals.</p> <p>23 BY MS. APPEL:</p> <p>24 Q. Earlier today you had mentioned</p>

<p style="text-align: right;">Page 346</p> <p>1 a shared file. Is that shared file something 2 that you created or plaintiffs' counsel 3 created? 4 A. It's something that I think 5 plaintiffs' counsel created for me to be able 6 to send them documents and receive documents, 7 and it's a Dropbox share file. It's -- at 8 this point I think it might be mine. I'm not 9 sure just exactly who's in charge of that or 10 runs it, but it comes directly into my 11 Dropbox file. 12 I know I had to boost my 13 subscription to Dropbox in order to hold the 14 2 gigabytes of data from -- that we were 15 putting into there. 16 Q. Is there anything from that 17 Dropbox file that you relied upon in forming 18 your opinion in your report that you have not 19 already provided to defense counsel? 20 A. No, everything that was in that 21 Dropbox that I've relied upon has been 22 identified here. 23 Q. Who prepared Exhibit B to your 24 report?</p>	<p style="text-align: right;">Page 348</p> <p>1 accumulating information in the draft as a 2 result of my review of the literature. 3 So if I had to separate things 4 out, I would say that, by far, the -- most of 5 the time has been spent in reading articles 6 and reviewing them and comparing them with 7 other articles, and a comparatively small 8 amount of time has been spent in drafting the 9 report. 10 Although there were some 11 strings of activity which was all report 12 drafting basically, I would say probably 85 13 to 90% was research, seeking articles, 14 reading them, reviewing them, and comparing 15 them. 16 Q. And you also testified earlier 17 today that you discarded information not 18 relevant or interesting to you. 19 How did you make that 20 determination? 21 MS. O'DELL: Objection to the 22 form. 23 A. The things that I discarded did 24 not seem to fit into my gestalt of the</p>
<p style="text-align: right;">Page 347</p> <p>1 A. Exhibit B was a list of 2 articles from the research literature 3 included in the Dropbox that -- that I think 4 does not -- I don't know whether it includes 5 the referenced articles from my report or 6 not, but they were all part of the same 7 collection of research articles and 8 supplemental documents. 9 Q. And my question, Dr. Carson, 10 was: Who prepared that exhibit? 11 A. The exhibit was prepared by the 12 plaintiffs' attorneys. 13 Q. You testified earlier that you 14 have spent approximately 150 to 180 hours in 15 your expert retention work; is that correct? 16 A. Correct. 17 Q. Can you estimate what portion 18 of that time was spent researching versus 19 what portion of time was spent actually 20 drafting your expert report? 21 A. Those two things are in some 22 ways difficult to separate because I would -- 23 I was writing my report the entire time that 24 I was reviewing the research materials and</p>	<p style="text-align: right;">Page 349</p> <p>1 understanding of this question and the 2 opinions that I wanted to express. They may 3 have been interesting information and useful 4 for some purposes, but not for this 5 particular report. 6 BY MS. APPEL: 7 Q. Was some of that information 8 that you discarded based on relevancy or that 9 you determined was not of interest 10 information that may have been different than 11 your opinions? 12 A. No. I didn't discard any 13 research because the opinions provided 14 differed from my own. These were things that 15 really were irrelevant to the question. 16 I remember finding an awful lot 17 of geological research stuff that just didn't 18 have any relevance to the question. 19 Because I used such broad 20 search terms, I ended up pulling in a whole 21 lot of things that were not necessary or 22 useful, and those just went in the trash. 23 Q. You testified earlier that you 24 have not treated any patients with ovarian</p>

<p style="text-align: right;">Page 350</p> <p>1 cancer; is that correct?</p> <p>2 A. Not knowingly, not because of</p> <p>3 ovarian cancer.</p> <p>4 Q. Have you ever diagnosed any</p> <p>5 patients with ovarian cancer?</p> <p>6 A. I think when I was in medical</p> <p>7 school or residency, I probably participated</p> <p>8 in that on several patients.</p> <p>9 Q. Have you ever instructed a</p> <p>10 patient not to use talcum powder products?</p> <p>11 A. I hadn't up until a month or</p> <p>12 two ago, but I've been asking people about --</p> <p>13 about their talcum powder use just as sort of</p> <p>14 a curiosity in mentioning that there might be</p> <p>15 a risk.</p> <p>16 Q. Do you ask that of all your</p> <p>17 patients?</p> <p>18 A. I would say no, I don't usually</p> <p>19 ask the men that, but I probably should.</p> <p>20 Q. And have the responses to those</p> <p>21 inquiries of your female patients and their</p> <p>22 talcum product use, has that been used at all</p> <p>23 to inform your opinions in this case?</p> <p>24 A. I don't think so. There have</p>	<p style="text-align: right;">Page 352</p> <p>1 usually administer to my patients, and I have</p> <p>2 plans to add that as a question in my</p> <p>3 environmental exposure survey. Which I</p> <p>4 haven't done already, but will as soon as I</p> <p>5 get the opportunity.</p> <p>6 BY MS. APPEL:</p> <p>7 Q. You testified earlier today</p> <p>8 that you do not believe there was ever a</p> <p>9 point where talcum powder did not contain</p> <p>10 asbestos, correct?</p> <p>11 A. Yes.</p> <p>12 Q. So in forming your opinion in</p> <p>13 your report, you've assumed that the talcum</p> <p>14 powder does contain asbestos, correct?</p> <p>15 MS. O'DELL: Object to the</p> <p>16 form.</p> <p>17 A. Well, I think the asbestos</p> <p>18 contribution to this whole issue is important</p> <p>19 and significant. I think there's good</p> <p>20 evidence that whatever we call talcum powder</p> <p>21 is carcinogenic and responsible for ovarian</p> <p>22 cancer -- as a cause of ovarian cancer, but I</p> <p>23 can't say -- I can't say based on looking at</p> <p>24 a can of talcum powder whether or not it has</p>
<p style="text-align: right;">Page 351</p> <p>1 been very few that I have asked that question</p> <p>2 in the last month or so. I've had a limited</p> <p>3 clinic schedule during this period of time.</p> <p>4 We had the holidays and other things, so I</p> <p>5 haven't seen that many patients.</p> <p>6 And of those I've asked about</p> <p>7 it, it seems about half of the women have had</p> <p>8 a history of using talcum powder.</p> <p>9 Q. And of those women that are</p> <p>10 using -- have told you that they have used</p> <p>11 talcum powder, are those women diagnosed with</p> <p>12 ovarian cancer?</p> <p>13 A. No.</p> <p>14 Q. So suffice to say the inquiry</p> <p>15 that you've asked of your female patients</p> <p>16 concerning their talcum use has nothing to do</p> <p>17 with the question that you've been posed in</p> <p>18 this particular litigation?</p> <p>19 MS. O'DELL: Object to the</p> <p>20 form.</p> <p>21 A. Actually, that's the only</p> <p>22 reason I've been asking them. It's not</p> <p>23 something that came to mind earlier. I have</p> <p>24 an environmental exposure survey that I</p>	<p style="text-align: right;">Page 353</p> <p>1 asbestos in it or how much.</p> <p>2 BY MS. APPEL:</p> <p>3 Q. Have you formed an opinion,</p> <p>4 Dr. Carson, on whether there's a relationship</p> <p>5 between pure talc and ovarian cancer?</p> <p>6 MS. O'DELL: Objection to form.</p> <p>7 A. My opinion is there is, but</p> <p>8 that's based on the research reports that</p> <p>9 have been done using so-called pure talc,</p> <p>10 talcum powder, and I am -- I -- my opinion is</p> <p>11 that it's unlikely that those test substances</p> <p>12 actually are pure talc.</p> <p>13 BY MS. APPEL:</p> <p>14 Q. So again, Dr. Carson, in</p> <p>15 forming your opinions, you have done so on</p> <p>16 the belief that all the talc powder products</p> <p>17 or just pure talc do, in fact, contain</p> <p>18 asbestos?</p> <p>19 MS. O'DELL: Objection to form.</p> <p>20 A. It is my opinion that all</p> <p>21 talcum powder products do contain a certain</p> <p>22 amount of asbestos, even if it's extremely</p> <p>23 small.</p> <p>24 My opinions have been formed</p>

<p style="text-align: right;">Page 354</p> <p>1 based on research that has been done on</p> <p>2 available talcum powder products, so I guess</p> <p>3 the research would have been done using some</p> <p>4 small quantity of asbestos in all of those</p> <p>5 studies.</p> <p>6 BY MS. APPEL:</p> <p>7 Q. You also testified today,</p> <p>8 Dr. Carson, that you have found in your</p> <p>9 research that there is a dose-response</p> <p>10 relationship between talcum powder products</p> <p>11 and ovarian cancer, correct?</p> <p>12 A. Well, a number of the research</p> <p>13 studies, the epidemiology studies have shown</p> <p>14 positive and statistically significant</p> <p>15 trends.</p> <p>16 Q. And those trends that you're</p> <p>17 relying on, Dr. Carson, actually only relate</p> <p>18 to duration and frequency, correct?</p> <p>19 MS. O'DELL: Objection to form.</p> <p>20 A. Yes, they do relate to duration</p> <p>21 and frequency, which is the only surrogate we</p> <p>22 have for dose.</p> <p>23 BY MS. APPEL:</p> <p>24 Q. So in forming your opinion,</p>	<p style="text-align: right;">Page 356</p> <p>1 classified by IARC.</p> <p>2 BY MS. APPEL:</p> <p>3 Q. But it's your opinion that a</p> <p>4 possible carcinogen -- strike that.</p> <p>5 It's your opinion that any dose</p> <p>6 of a possible carcinogen can cause cancer?</p> <p>7 MS. O'DELL: Objection to form.</p> <p>8 A. Yes, I think there is a</p> <p>9 potential for any dose of a carcinogen to</p> <p>10 cause a cancer. There's also the principle</p> <p>11 that the lower the dose, the less likely it</p> <p>12 is, the lower the risk is for developing a</p> <p>13 cancer.</p> <p>14 BY MS. APPEL:</p> <p>15 Q. And your opinion extends to</p> <p>16 those particles that have not been identified</p> <p>17 as carcinogens, but may just be possible</p> <p>18 carcinogens?</p> <p>19 A. I think talc has been</p> <p>20 identified as a carcinogen.</p> <p>21 Q. So you disagree with the IARC</p> <p>22 classification?</p> <p>23 A. The IARC 2B classification is a</p> <p>24 carcinogenic classification.</p>
<p style="text-align: right;">Page 355</p> <p>1 Dr. Carson, you have not determined a level</p> <p>2 of harmful exposure to talcum powder products</p> <p>3 that causes ovarian cancer?</p> <p>4 A. That's correct.</p> <p>5 Q. And you did not conduct a dose</p> <p>6 assessment between talcum powder products and</p> <p>7 ovarian cancer, correct?</p> <p>8 MS. O'DELL: Objection to form.</p> <p>9 A. Well, I did not conduct a</p> <p>10 dose-response, but I am of the opinion that</p> <p>11 there's no safe threshold for exposure to a</p> <p>12 carcinogen until such a threshold is</p> <p>13 identified.</p> <p>14 BY MS. APPEL:</p> <p>15 Q. And does that include</p> <p>16 Category 2B particles as well --</p> <p>17 MS. O'DELL: Objection.</p> <p>18 BY MS. APPEL:</p> <p>19 Q. -- that it's a possible</p> <p>20 carcinogen?</p> <p>21 MS. O'DELL: Objection to form.</p> <p>22 A. It includes the talc that was</p> <p>23 discussed in the IARC report. Those</p> <p>24 conclusions have nothing to do with how it's</p>	<p style="text-align: right;">Page 357</p> <p>1 Q. But you recognize and -- that</p> <p>2 there are different types of categories that</p> <p>3 IARC has?</p> <p>4 A. Yes.</p> <p>5 Q. And that -- it's that talc that</p> <p>6 does not contain asbestos was not, in fact,</p> <p>7 categorized as a Group 1, correct?</p> <p>8 A. That's correct.</p> <p>9 Q. So is it your opinion, then,</p> <p>10 looking at other 2B-classified particles by</p> <p>11 IARC, that any exposure to pickled vegetables</p> <p>12 would cause cancer?</p> <p>13 A. We know that there are a number</p> <p>14 of carcinogens that are regularly present in</p> <p>15 things like the food that we eat. We have a</p> <p>16 rule that says that those things should not</p> <p>17 be included in food items unless they have</p> <p>18 passed a particular exemption process.</p> <p>19 Pickled vegetables are</p> <p>20 something that people have been familiar with</p> <p>21 and have been using for hundreds of years,</p> <p>22 and things like talcum powder are things that</p> <p>23 have been used for -- well, at least a</p> <p>24 hundred years, but probably considerably</p>

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1 longer.

2 And whether or not those things

3 are carcinogens, there are people who still

4 find enough value to offset that factor in

5 their own lives and they can make their own

6 decisions regarding their exposure.

7 It's a similar concept to

8 people who choose to smoke. Although smoking

9 is an addictive behavior, people are aware

10 that it causes disease, including cancer, and

11 yet they continue to smoke.

12 We continue to eat grilled

13 meats, even -- most of us know now that

14 grilled meats contain polycyclic aromatic

15 hydrocarbons that are known carcinogens, some

16 of them Group 1 carcinogens, and yet, we

17 continue that practice and revel in it even.

18 That's just part of what we do as human

19 beings.

20 The issue with talc is a

21 complicated question in my mind. I think I'm

22 straying a bit from your -- from your

23 question, but baby powder, for example, is

24 something that has a very -- very dear sort

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1 of relationship to many people.

2 The experience with that from

3 the time you were a baby until you grow up

4 and have your own children involves a lot of

5 the use of baby powder in many, many

6 households. That's a difficult relationship

7 to break. It's psychological as much as it

8 is knowledge based.

9 So as we go through the

10 decades, we get a little safer and safer as

11 we begin to peel these habits, these

12 dangerous habits away from our lives and

13 accept better lifestyles.

14 MR. ZELLERS: Move to strike as

15 nonresponsive.

16 MS. APPEL: Respectfully --

17 MS. BOCKUS: Is he finished?

18 MR. ZELLERS: I don't think so.

19 THE WITNESS: I can go on.

20 BY MS. APPEL:

21 Q. Yeah. My question was more

22 narrow, and I was analogizing your opinion as

23 to talcum powder and was asking about other

24 2B classifications, and my example --

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1 A. Pickled vegetables.

2 Q. -- I had was pickled

3 vegetables, and the question was whether or

4 not is your opinion that any consumption of

5 pickled vegetables causes cancer?

6 MS. O'DELL: Objection to form.

7 A. I believe the primary form of

8 cancer that's potentially related with

9 pickled vegetables is stomach cancer, and

10 there is a slight increase in risk with

11 consumption of pickled vegetables for

12 everybody who does it.

13 BY MS. APPEL:

14 Q. Okay. And what about gasoline

15 or exhaust?

16 A. Gasoline meaning the fuel?

17 Q. Yes.

18 A. Well, gasoline used to contain

19 a significant amount of benzene, which was

20 a -- determined to be a carcinogenic

21 substance. In recent years, most of the

22 benzene has been removed from gasoline, so

23 now there's very little benzene in vapors

24 that are expressed.

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1 But there's a small amount. So

2 when you inhale gasoline vapors, you are also

3 exposing yourself to a very small amount of a

4 carcinogenic substance.

5 As far as exhaust is concerned,

6 diesel exhaust in particular has -- contains

7 particles that have been identified through

8 various bioassays to be carcinogenic. So

9 diesel exhaust is regulated as a carcinogenic

10 material, even though we continue to be

11 exposed.

12 Q. And it's your opinion that any

13 exposure that we all incur related to exhaust

14 will cause us cancer?

15 MS. O'DELL: Objection to form.

16 A. It will cause an increase in

17 risk of cancer. Doesn't necessarily cause

18 cancer in everybody.

19 BY MS. APPEL:

20 Q. Okay. Are you aware that Saed

21 has been hired by plaintiffs' counsel in this

22 litigation?

23 A. I am. And when I misspoke

24 earlier today regarding the Taher paper, I

<p style="text-align: right;">Page 362</p> <p>1 was thinking of the Saed paper.</p> <p>2 Q. Okay. Last question: Counsel</p> <p>3 was asking you about the migration process,</p> <p>4 and you mentioned that in the course of</p> <p>5 particles moving up the track, that some of</p> <p>6 it may come back out even after it reaches</p> <p>7 the fluid surrounding the ovaries, correct?</p> <p>8 A. Yes.</p> <p>9 Q. So if particles have the</p> <p>10 ability to come back out, that means that</p> <p>11 there is, in fact, some form of an intrinsic</p> <p>12 elimination system.</p> <p>13 A. Well, if this is all based on</p> <p>14 mass action, it would not necessarily be an</p> <p>15 intrinsic elimination system, and I believe</p> <p>16 that talc particles, once they produce an</p> <p>17 inflammatory response, they become</p> <p>18 sequestered within that inflammatory milieu</p> <p>19 and no longer are available for movement back</p> <p>20 out into the fluid.</p> <p>21 I'm sure there's some small</p> <p>22 percentage of them that are an exception to</p> <p>23 that, but for the majority, that would be the</p> <p>24 case.</p>	<p style="text-align: right;">Page 364</p> <p>1 CERTIFICATE</p> <p>2 I, MICHAEL E. MILLER, Fellow of</p> <p>3 the Academy of Professional Reporters,</p> <p>4 Registered Diplomate Reporter, Certified</p> <p>5 Realtime Reporter, Certified Court Reporter</p> <p>6 and Notary Public, do hereby certify that</p> <p>7 prior to the commencement of the examination,</p> <p>8 ARCH I. "CHIP" CARSON, M.D., Ph.D. was duly</p> <p>9 sworn by me to testify to the truth, the</p> <p>10 whole truth and nothing but the truth.</p> <p>11 I DO FURTHER CERTIFY that the</p> <p>12 foregoing is a verbatim transcript of the</p> <p>13 testimony as taken stenographically by and</p> <p>14 before me at the time, place and on the date</p> <p>15 hereinbefore set forth, to the best of my</p> <p>16 ability.</p> <p>17 I DO FURTHER CERTIFY that pursuant</p> <p>18 to FRCP Rule 30, signature of the witness was</p> <p>19 not requested by the witness or other party</p> <p>20 before the conclusion of the deposition.</p> <p>21 I DO FURTHER CERTIFY that I am</p> <p>22 neither a relative nor employee nor attorney</p> <p>23 nor counsel of any of the parties to this</p> <p>24 action, and that I am neither a relative nor</p> <p>employee of such attorney or counsel, and</p> <p>that I am not financially interested in the</p> <p>action.</p> <p>MICHAEL E. MILLER, FAPR, RDR, CRR Fellow of the Academy of Professional Reporters NCRA Registered Diplomate Reporter NCRA Certified Realtime Reporter Certified Court Reporter</p> <p>Notary Public in and for the State of Texas My Commission Expires: 7/9/2020</p> <p>Dated: January 22, 2019</p>
<p style="text-align: right;">Page 363</p> <p>1 MS. APPEL: Okay. That's all I</p> <p>2 have. Thank you, Dr. Carson.</p> <p>3 MS. TINSLEY: I don't have any</p> <p>4 questions.</p> <p>5 MS. O'DELL: Okay. Why don't</p> <p>6 we take a short break.</p> <p>7 THE VIDEOGRAPHER: Off the</p> <p>8 record at 5:37, end of Tape 4.</p> <p>9 (Recess taken, 5:37 p.m. to</p> <p>10 5:44 p.m.)</p> <p>11 THE VIDEOGRAPHER: We're on the</p> <p>12 record at 5:44, beginning of Tape 5.</p> <p>13 MS. O'DELL: Dr. Carson, I</p> <p>14 don't have any questions, so this will</p> <p>15 conclude your deposition.</p> <p>16 MR. ZELLERS: Thank you,</p> <p>17 Doctor.</p> <p>18 THE VIDEOGRAPHER: Going off</p> <p>19 the record, 5:44. End of deposition,</p> <p>20 end of Tape 5.</p> <p>21 (Proceedings recessed at</p> <p>22 5:45 p.m.)</p> <p>23 --o0o--</p> <p>24</p>	<p style="text-align: right;">Page 365</p> <p>1 INSTRUCTIONS TO WITNESS</p> <p>2</p> <p>3 Please read your deposition over</p> <p>4 carefully and make any necessary corrections.</p> <p>5 You should state the reason in the</p> <p>6 appropriate space on the errata sheet for any</p> <p>7 corrections that are made.</p> <p>8 After doing so, please sign the</p> <p>9 errata sheet and date it.</p> <p>10 You are signing same subject to</p> <p>11 the changes you have noted on the errata</p> <p>12 sheet, which will be attached to your</p> <p>13 deposition.</p> <p>14 It is imperative that you return</p> <p>15 the original errata sheet to the deposing</p> <p>16 attorney within thirty (30) days of receipt</p> <p>17 of the deposition transcript by you. If you</p> <p>18 fail to do so, the deposition transcript may</p> <p>19 be deemed to be accurate and may be used in</p> <p>20 court.</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p>

Page 366		Page 368	
1	ERRATA	1	LAWYER'S NOTES
2	PAGE LINE CHANGE	2	
3		3	PAGE LINE
4	REASON: _____	4	_____
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23		23	_____
24	REASON: _____	24	_____
Page 367			
1	ACKNOWLEDGMENT OF DEPONENT		
2			
3			
4	I, ARCH I. "CHIP" CARSON, M.D.,		
5	Ph.D., do hereby certify that I have read the		
6	foregoing pages and that the same is a		
7	correct transcription of the answers given by		
8	me to the questions therein propounded,		
9	except for the corrections or changes in form		
10	or substance, if any, noted in the attached		
11	Errata Sheet.		
12			
13	ARCH I. "CHIP" CARSON, M.D., Ph.D. DATE		
14			
15	Subscribed and sworn to before me this		
16	_____ day of _____, 20 ____.		
17	My commission expires: _____		
18			
19	_____		
20	Notary Public		
21			
22			
23			
24			

Exhibit 32

Shawn Levy, Ph.D.

Page 1

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF NEW JERSEY

IN RE: JOHNSON & JOHNSON
TALCUM POWDER PRODUCTS
MARKETING, SALES PRACTICES,
AND PRODUCTS LIABILITY
LITIGATION

Case No. 16-2738

THIS DOCUMENT RELATES TO (FLW) (LHG)
ALL CASES
MDL Docket No. 2738

Friday, January 11, 2019

- - - - -

The video deposition of SHAWN LEVY, Ph.D.,
taken pursuant to notice, was held at the
Embassy Suites Huntsville, 850 Monroe Street
S.W., Huntsville, Alabama, commencing at
approximately 9:04 a.m., on the above date,
before Lois Anne Robinson, Registered Diplomat
Reporter, Certified Realtime Reporter, and
Notary Public for the State of Alabama.

Shawn Levy, Ph.D.

Page 2

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Shawn Levy, Ph.D.

Page 3

1 A P P E A R A N C E S - (continued)

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JULIE ROBINSON

19

20

21

LOIS ANNE ROBINSON, RPR, RDR, CRR
COURT REPORTER

22

23

24

Shawn Levy, Ph.D.

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1 I N D E X

2 EXAMINATION PAGE

3

4 By Ms. Brown 7

5 By Mr. Ferguson 307

6 By Ms. O'Dell 357

7 By Ms. Brown 372

8 By Ms. O'Dell 389

9

10 * * * * *

11

12 EXHIBITS

13 Deposition Exhibit Number 1 14

14 Notice of Deposition

15 Deposition Exhibit Number 2 33

16 Levy expert report

17 Deposition Exhibit Number 3 16

18 Levy invoices of 5/2/18 and 1/8/19

19 Deposition Exhibit Number 4 19

20 Government of Canada document regarding draft screening

21 assessment of talc

22 Deposition Exhibit Number 5 21

23 Government of Canada document regarding potential risk of

24 lung effects and ovarian cancer from talc

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1	I N D E X - (Continued)	
2	Deposition Exhibit Number 6	23
3	Draft manuscript regarding systematic review and	
4	meta-analysis of the association between perineal use of talc	
5	and risk of ovarian cancer	
6	Deposition Exhibit Number 7	30
7	Hamilton article	
8	Deposition Exhibit Number 8	49
9	Judith Zelikoff expert report	
10	Deposition Exhibit Number 9	59
11	Mayo Clinic website article entitled "Cancer"	
12	Deposition Exhibit Number 10	72
13	Wikipedia page	
14	Deposition Exhibit Number 11	75
15	Coussens and Werb article	
16	Deposition Exhibit Number 12	82
17	Preprint manuscript of "Molecular Basis Supporting the	
18	Association of Talcum Powder Use With Increased Risk of	
19	Ovarian Cancer"	
20	Deposition Exhibit Number 13	82
21	December 26 Email to Dr. Saed	
22	Deposition Exhibit Number 14	142
23	"Evaluating Biological Plausibility in Supporting Evidence	
24	For Action Through Systematic Reviews in Public Health"	

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1	I N D E X - (continued)	
2	Deposition Exhibit Number 15	190
3	NTP study	
4	Deposition Exhibit Number 16	192
5	2014 Citizens Petition to FDA	
6	Deposition Exhibit Number 17	208
7	Buz'Zard study	
8	Deposition Exhibit Number 18	218
9	"Perineal Talc Use and Ovarian Cancer," by Ross Penninkilampi	
10	Deposition Exhibit Number 19	249
11	Heller article	
12	Deposition Exhibit Number 20	270
13	Merritt paper - "Talcum Powder Chronic Pelvic Inflammation	
14	and NSAIDs in Relation to the Risk of Epithelial Ovarian	
15	Cancer"	
16	Deposition Exhibit Number 21	326
17	Nunes article	
18	Deposition Exhibit Number 22	367
19	Park article	
20		
21		
22		
23		
24		

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1 VIDEOGRAPHER:

2 We are now on the record. My name is
3 Julie Robinson. I'm a videographer representing
4 Golkow Litigation Services.

5 Today's date is January 11th, 2019, and
6 the time is 9:04 a.m.

7 This video deposition is being held in
8 Huntsville, Alabama, in the matter of
9 Johnson & Johnson Talcum Powder Product Marketing,
10 Sales Practices, and Products Liability
11 Litigation, MDL Docket Number 2738.

12 The deponent is Dr. Shawn Levy.

13 Counsel will be noted on the
14 stenographic record.

15 The court reporter is Lois Robinson,
16 who will now swear in the witness.

17 SHAWN LEVY, Ph.D.,
18 the witness, after having first been
19 duly sworn to tell the truth, the whole truth,
20 and nothing but the truth, was examined and
21 testified as follows:

22 EXAMINATION

23 BY MS. BROWN:

24 Q Good morning, Dr. Levy.

Shawn Levy, Ph.D.

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1 A Good morning.

2 Q My name is Alli Brown. I represent
3 Johnson & Johnson, and I'll start with some
4 questions for you here today.

5 Dr. Levy, have you ever been deposed
6 before?

7 A Yes.

8 Q And tell me, how many times?

9 A In a setting like this, once.

10 Q Okay. What was the nature of that
11 deposition?

12 A It was a patent litigation case.

13 Q Were you serving as an expert witness
14 in that case?

15 A I was.

16 Q Were you hired by the plaintiffs or the
17 defendants?

18 A The plaintiffs.

19 Q And, just generally, what were the
20 issues in that case?

21 A It was entirely focused on evaluation
22 of prior art in the genomic space.

23 Q And any time --

24 And do you remember the name of that

Shawn Levy, Ph.D.

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1 case, by the way?

2 A I don't. It was, gosh, twelve years
3 ago or so.

4 Q I see.

5 Did that case go to trial?

6 A Not that I'm aware of.

7 Q Have you ever testified at trial?

8 A I have not.

9 Q Okay. And other than that one patent
10 case you just described for us, were there other
11 depositions that you've given?

12 A No.

13 Q And I think, when you started to answer
14 the question in the beginning, you said "in a
15 setting like this." Is there another time, in
16 your mind, where you've given testimony under
17 oath?

18 A No, not under oath. That's why I
19 was --

20 So I've had a number of meetings, all
21 limited to the patent space of mainly prior art
22 discussions, where there's been representatives
23 from both sides where we were having a
24 discussion. But it wasn't a formal deposition

1 with a court reporter, under oath, et cetera.

2 Q Understood.

3 So this would then be the second time
4 you've been deposed in a setting like this.

5 A Correct.

6 Q Is that fair?

7 Okay. So a few ground rules that you
8 may already be familiar with from your prior
9 experience. First, we'll try not to speak over
10 each other. Is that fair?

11 A That's fair.

12 Q That way, our court reporter can get
13 down all my questions and all your answers.

14 Okay?

15 A (Nods affirmatively.)

16 Q If you don't understand a question of
17 mine, will you let me know?

18 A I will.

19 Q Okay. Try to verbalize your answers,
20 too, so our court reporter can take them down.

21 Okay?

22 A Understood.

23 Q Okay. If you need a break, let me
24 know, and we'll be happy to accommodate you.

Shawn Levy, Ph.D.

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1 Do you understand you're under oath
2 here today, same as if you were in a court of
3 law?

4 A I do.

5 Q Okay. I am --

6 And, before we get started, Doctor, I
7 see you have a couple of items in front of you,
8 and I want to identify what we have for the
9 record.

10 To your right is an iPad that is
11 showing the realtime of my questions and your
12 answers. Will you be using that to assist you in
13 your testimony here today?

14 A Yes.

15 Q Okay. In front of you you have a
16 laptop computer.

17 A (Nods affirmatively.)

18 Q Will you be using that to assist you in
19 your testimony?

20 A Yes.

21 Q And tell me, is this your laptop?

22 A It is not.

23 Q Okay. Whose laptop is it?

24 A The -- the attorneys I've been working

1 with.

2 Q Okay. In front of you is the
3 plaintiffs' lawyer's laptop. Is that right?

4 A That's right.

5 Q Okay. And what is contained on the
6 plaintiffs' lawyer's laptop?

7 MS. O'DELL:

8 I think I'd probably be better to speak
9 to it.

10 MS. BROWN:

11 No, no. Let's get it from the witness,
12 and then if you want to make a statement for the
13 record, of course.

14 Q Let's -- let's get your understanding
15 of what's on this laptop in front of you.

16 A Other than what's on the USB drive that
17 I've been using, I -- I don't have any knowledge
18 of what's on it.

19 Q Okay. Do you know what's on the USB
20 drive?

21 A I do.

22 Q What's that?

23 A It's a collection of literature cited
24 in reliance literature list that -- from

Shawn Levy, Ph.D.

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1 my -- from my report.

2 Q Did you put together the items that are
3 contained on the USB drive that you have in front
4 of you?

5 MS. O'DELL:

6 Object to the form.

7 A Yes.

8 MS. BROWN:

9 Q Is that your USB drive?

10 A No. I put together the list.

11 As far as who moved the files and
12 organized the files on the USB, that, I don't
13 know.

14 Q Okay. Are all of the files on that USB
15 drive documents that you considered in connection
16 with your opinion in this case?

17 A They are.

18 Q Any other materials in front of you
19 that you'll be using to assist you in your
20 testimony here today?

21 A There's a -- I have a hard copy of my
22 report.

23 Q Did you prepare that hard copy binder?

24 A No.

Shawn Levy, Ph.D.

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1 Q Who -- who did?

2 A My -- the -- the attorneys I've been
3 working with. So I -- they -- they provided the
4 printout and the nice binder that it's in.

5 Q Okay. Did you, Doctor, make any notes
6 on the report that you have in front of you?

7 A No.

8 Q Okay. I'm gonna hand you what we have
9 marked as Exhibit 1 to your deposition, which is
10 a notice of your deposition.

11 (DEPOSITION EXHIBIT NUMBER 1
12 WAS MARKED FOR IDENTIFICATION.)

13 MS. BROWN:

14 Q And I'll ask, is this something that
15 you have ever seen before?

16 A Yes.

17 Q When did you see it?

18 A I'd have to review my email, but it was
19 some -- sometime ago, some weeks ago.

20 Q Okay. Have you brought any --

21 And you understand that this Notice of
22 Deposition that we've marked as Exhibit 1
23 requests that you bring certain documents with
24 you here today?

Shawn Levy, Ph.D.

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1 A Yes.

2 Q Okay.

3 MS. O'DELL:

4 Let me just insert for the record,
5 we've objected to certain requests contained in
6 the notice, and objections have been served, and
7 materials have been brought to this deposition
8 consistent with those objections.

9 MS. BROWN:

10 And we are in receipt of your
11 objections.

12 Q And your counsel for the plaintiffs
13 represented that some materials have been brought
14 to the deposition. Do you have any materials
15 with you responsive to this notice?

16 A Well --

17 MS. O'DELL:

18 I'll provide to you invoices that are
19 responsive to the Notice, and there are materials
20 that Dr. Levy has seen since his report was
21 served, and -- and those are copies.

22 MS. BROWN:

23 Thank you, counsel.

24 Q So, Doctor, let's start --

Shawn Levy, Ph.D.

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1 Thank you.

2 -- by marking these, and I'll ask you
3 some questions about what we have.

4 (DEPOSITION EXHIBIT NUMBER 3
5 WAS MARKED FOR IDENTIFICATION.)

6 MS. BROWN:

7 Q I'll mark as Exhibit 3 to your
8 deposition two invoices counsel for plaintiffs
9 just handed me, one dated May 2nd, 2018, and the
10 other dated January 8th, 2019. And we only have
11 one copy, so let me hand it to you and ask you,
12 are these invoices that you created, Doctor?

13 A They are.

14 Q Okay. And I want to take that back for
15 one second.

16 Looks like the first entry on your
17 invoice is dated May 16th, 2017. Does that sound
18 right to you?

19 A That sounds right.

20 Q When were you first approached about an
21 involvement in this case?

22 A Earlier in 2017.

23 Q Okay. And who approached you?

24 A Leigh and Jennifer. I'd have to verify

Shawn Levy, Ph.D.

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1 in my email whom I may have heard from first.

2 Q Okay. And Leigh and Jennifer are
3 counsel for plaintiffs in this litigation; is
4 that right?

5 A That's right.

6 Q And did they -- had you known them
7 prior to receiving contact early in 2017 --

8 A No.

9 Q -- from plaintiffs' lawyers?

10 A I -- I did not know them.

11 Q Did they call you at your place of
12 business?

13 A I believe the first contact was email.
14 But, ultimately, yes.

15 Q Okay. And was there any connection,
16 meaning did someone refer the plaintiffs' lawyers
17 to you, or do you know?

18 A I don't know.

19 Q Do you have any idea how the
20 plaintiffs' lawyers found you?

21 A I do not.

22 Q Okay. It looks like, Doctor, that
23 these two invoices have a total of 33 hours.
24 Does that sound right to you?

Shawn Levy, Ph.D.

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1 A It does.

2 Q Looks like something's blacked out on
3 the second page of the invoices. Do you know
4 what that is?

5 MS. O'DELL:

6 I'll just say that redactions were made
7 by counsel. They referenced the subject matter
8 of conversations between Dr. Levy and counsel,
9 and those have been redacted because of work
10 product privilege.

11 MS. BROWN:

12 Okay.

13 Q Is it fair, Doctor, that you've spent a
14 total of 33 hours forming your opinions in this
15 case?

16 A That's fair.

17 Q Okay. Do you have any additional
18 invoices that you plan to submit to the lawyers
19 for the plaintiffs?

20 A Yes.

21 Q Okay. And can you ballpark for me how
22 much additional time you've spent since the last
23 entry here, which appears to be December 12th,
24 2018?

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1 A There's probably another -- not
2 including this morning -- roughly 15 hours.

3 Okay. I'll hand you, Doctor, what we
4 have marked as Exhibit 4 to your deposition.
5 This is another document counsel for the
6 plaintiffs just handed me.

7 (DEPOSITION EXHIBIT NUMBER 4
8 WAS MARKED FOR IDENTIFICATION.)

9 MS. BROWN:

10 Q Would you identify that for the record,
11 please.

12 A This is a printed copy from a website
13 from the government of Canada discussing their
14 draft screening assessment of talc.

15 Q Okay. Is that something you've seen
16 before today?

17 A Yes.

18 Q When did you see it first?

19 A Sometime in December.

20 Q Did the lawyers for plaintiffs give it
21 to you?

22 A They did.

23 Q Okay. Your report in this case --
24 Can I have that back?

Shawn Levy, Ph.D.

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1 Your report in this case was served in
2 November of 2018; correct?

3 A Correct.

4 Q Fair to say, then, that Exhibit 4,
5 which you saw for the first time in December of
6 2018, did not inform the opinions contained in
7 your report?

8 A That's correct.

9 Q Okay. Did the -- does Exhibit 4
10 contain any information regarding chronic
11 inflammation as the proposed mechanism of ovarian
12 cancer induced by talc?

13 A I don't believe it does. I'd have to
14 review -- take a look at it to be sure.

15 MS. O'DELL:

16 And if you need to look at it, I'm sure
17 counsel will hand it to you.

18 MS. BROWN:

19 Q I'm handing you, Doctor --

20 MS. O'DELL:

21 Excuse me. If you need to look at it
22 to answer that question, you may.

23 A To be sure I'm accurate in my answer,
24 I'd like to take a look at that.

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1 MS. BROWN:

2 Q Sure. Sitting here --

3 Hold on.

4 Sitting here today, you're not aware if

5 Exhibit 4 contains any information regarding the

6 proposed mechanism of chronic inflammation as a

7 cause for ovarian cancer?

8 MS. O'DELL:

9 Object to the question.

10 If you need to see the document,

11 Doctor, you may ask for it.

12 A Yeah. I'm not -- I'm not able to

13 answer it accurately without seeing the document.

14 (DEPOSITION EXHIBIT NUMBER 5

15 WAS MARKED FOR IDENTIFICATION.)

16 MS. BROWN:

17 Q Okay. Handing you what we've marked as

18 Exhibit 5, would you tell me what that is,

19 Doctor?

20 A This is another document from the

21 government -- government of Canada discussing the

22 potential risk of lung effects and ovarian cancer

23 from talc.

24 Q Is Exhibit 5 a final document, do you

1 know?

2 MS. O'DELL:

3 Object to the form.

4 A Yeah. That -- I don't -- I don't have
5 the information available to answer that
6 accurately.

7 MS. BROWN:

8 Q Have you seen Exhibit 5 prior to this
9 morning?

10 A I have.

11 Q When did you first see Exhibit 5?

12 A Similar in time to the earlier report
13 or this -- yes. Similar in time to the
14 earlier -- to the same document from Exhibit 4.

15 Q To the best of your recollection,
16 Doctor, you first saw Exhibit 5 after completing
17 your report in this matter; is that right?

18 A That is right.

19 Q Fair to say, then, that Exhibit 5 did
20 not inform the opinions contained in your MDL
21 report?

22 A That's correct.

23 Q Handing you, Doctor, what we've marked
24 as Exhibit 6 to your deposition, another document

1 counsel provided, counsel for plaintiffs provided
2 in response to your deposition notice.

3 (DEPOSITION EXHIBIT NUMBER 6
4 WAS MARKED FOR IDENTIFICATION.)

5 MS. BROWN:

6 Q Would you identify for the record
7 Exhibit 6?

8 A So this is a draft manuscript or
9 preprint manuscript that's been submitted for
10 peer review discussing the systematic review and
11 meta-analysis of the association between perineal
12 use of talc and risk of ovarian cancer.

13 Q Had you seen Exhibit 6 prior to this
14 morning?

15 A Yes.

16 Q When did you first see Exhibit 6?

17 A It was in December as well.

18 Q Exhibit 6 did not inform your opinions
19 in this matter. Fair?

20 A They did not inform the content of the
21 report.

22 Q Have you reviewed and analyzed Exhibit
23 6 since December?

24 A I have.

1 Q Does Exhibit 6 contain any information
2 regarding the proposed mechanism of chronic
3 inflammation?

4 A It does in reference, I believe. I'm
5 reminding myself if -- if it shared the same
6 materials that I had referenced in my report.

7 So, yes, it does.

8 Q Are you looking at a particular page,
9 Doctor?

10 A I am.

11 Q And would you identify that for the
12 record.

13 A I'm looking at page 23, beginning at
14 line 220.

15 Q And what information does Exhibit 6 at
16 page 23 contain regarding chronic inflammation?

17 A It discusses inflammation of the
18 epithelial ovarian surfaces in animal models and
19 provides two different references.

20 Q And were those references information
21 you considered in forming your opinions in this
22 case?

23 A Let me make sure of that.

24 Yes.

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1 Q And would you state what they are for
2 the record, please?

3 A One reference is T.C. Hamilton, et al.,
4 The British Journal of Experimental Pathology,
5 from 1984.

6 And the other reference is "The
7 Pathology of Ovarian" -- "The Pathology of
8 Ovarian Cancer Precursors," which is a review of
9 R.E. Scully in the Journal of Cellular
10 Biochemistry, and that is a supplement from 1995.
11 The latter is not referenced in my report.

12 Q Have you reviewed the Scully paper in
13 connection with your opinions in this matter?

14 A Not specifically, no.

15 Q You have, however, reviewed the
16 Hamilton paper?

17 A Yes.

18 Q You would agree that the Hamilton paper
19 does not show inflammation leading to neoplastic
20 changes in animals?

21 MS. O'DELL:

22 Object to the form.

23 A I'd have to see the manu- -- or the
24 manuscript to answer your specific question

1 regarding neoplasm.

2 MS. BROWN:

3 Q Does the Hamilton paper support your
4 view that chronic inflammation is a plausible
5 mechanism for talc-induced ovarian cancer?

6 A It supports my opinion that
7 inflammation is a component in the progression to
8 ovarian cancer.

9 Q Is it your testimony that the Hamilton
10 paper supports your opinion that chronic
11 inflammation leads to neoplastic changes?

12 A No, not necessarily.

13 Q Okay. Tell me how it is that the
14 Hamilton paper supports your opinion that chronic
15 inflammation can cause ovarian cancer.

16 A Well, the -- so my opinion regarding --
17 that the role of inflammation in ovarian cancer
18 is not based on a single study, particularly one
19 that is now approaching or is now over 30 years
20 old.

21 Q Okay. Does --

22 A So it's a -- I reviewed the -- that
23 paper as well as a large number or the totality
24 of the available evidence stretching across many

1 years to develop the opinion that's represented
2 in my report.

3 Q Sure.

4 A And to that opinion is -- no one study
5 or one singular piece of information is the basis
6 of that opinion.

7 Q Okay. But, you know, having reviewed
8 Hamilton, that what Hamilton shows is that the
9 inflammation they saw in the animals was not
10 associated with neoplastic changes. Right?

11 MS. O'DELL:

12 Excuse me.

13 Doctor, if you'd like to -- to pull up
14 Hamilton, you may do that.

15 MS. BROWN:

16 Q And we'll certainly give you time to do
17 that, Doctor.

18 Sitting here today, do you recall that
19 to be the conclusion of Hamilton?

20 MS. O'DELL:

21 Object to the form.

22 You don't -- if you need to see the --

23 MS. BROWN:

24 Counsel --

1 MS. O'DELL:

2 -- paper in order to answer the
3 question --

4 MS. BROWN:

5 Counsel --

6 MS. O'DELL:

7 -- you may do that.

8 MS. BROWN:

9 Counsel, he is absolutely entitled to
10 get the paper. We're going to do that.

11 Q Sitting here today, do you recall --

12 MS. O'DELL:

13 But he is not --

14 MS. BROWN:

15 It's a fair question.

16 MS. O'DELL:

17 Is it not a fair question.

18 MS. BROWN:

19 I'm not gonna --

20 MS. O'DELL:

21 He's asking --

22 MS. BROWN:

23 -- do this with you.

24 MS. O'DELL:

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1 Yes, you are. If he's asked to see the
2 paper, he gets to look at the paper. Because
3 this is not a situation where you can say, "Oh,
4 I'll show it to you later," ask all these
5 questions, try to get him to answer when he said
6 I want to see the paper and review it. That's
7 the way this works.

8 MS. BROWN:

9 Q Dr. Levy, can you answer the question
10 without looking at the paper?

11 MS. O'DELL:

12 Would you repeat the question just to
13 make sure we've got it?

14 MS. BROWN:

15 Yes. Would you please keep your
16 objections to form in accordance with the federal
17 rules?

18 MS. O'DELL:

19 My objections have been in accordance
20 with the federal rules.

21 MS. BROWN:

22 Q Dr. Levy, my question to you was
23 whether the Hamilton paper, the findings of the
24 Hamilton paper show that chronic inflammation led

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1 to neoplastic changes. Do you recall that
2 question?

3 A I do recall the question.

4 Q Can you answer that question without
5 looking at the paper?

6 A I would need to look at the paper to
7 accurately answer your question.

8 Q Absolutely. Do you have a copy on your
9 computer?

10 A I do.

11 Q Okay. We'll mark it, so we're all on
12 the same page, as Exhibit 7.

13 (DEPOSITION EXHIBIT NUMBER 7
14 WAS MARKED FOR IDENTIFICATION.)

15 MS. BROWN:

16 Q Here's a hard copy, Doctor, if that
17 assists you.

18 Doctor, looking at the Hamilton article
19 that you have in front of you, does that refresh
20 you that the authors found no association between
21 the talc-induced changes and neoplasm?

22 A No. Their -- their conclusions were
23 that the talc-induced changes -- specifically
24 fibrosis and the papillary changes -- did not

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1 appear to be a reaction to talc, but they -- I
2 don't see the specific inclusion that you asked
3 in the question regarding neoplasm.

4 Q I'm looking at page 103, Doctor, the
5 first full paragraph that begins "no evidence."

6 You with me?

7 A One moment. "No evidence of cellular,"
8 that paragraph?

9 Q Yes.

10 And, for the record, that paragraph
11 reads, "No evidence of cellular atypia or mitotic
12 activity was seen in the nonpapillary areas of
13 the surface epithelium of the injected ovaries
14 and in no ovary was there any evidence of frank
15 neoplasia."

16 Correct?

17 A It does read that way, yes.

18 Q And that was a conclusion of the
19 Hamilton article. Correct?

20 MS. O'DELL:

21 Object to the form.

22 A That was an observation of the Hamilton
23 article.

24 MS. BROWN:

1 Q The Hamilton article does not support
2 the theory that chronic inflammation leads to
3 neoplastic changes in the ovary. Fair?

4 MS. O'DELL:

5 Object to the form.

6 A The Hamilton article looked at an
7 interval of one month, eighteen months, in a rat
8 model. And, so, in the constraints of that
9 particular experimental design and given the
10 state of the art of the technology at the time,
11 the authors did not conclude of a significant
12 progression of ovarian cancer. But there's
13 clearly limitations in both their experimental
14 design and time course of the study to draw wide
15 conclusions.

16 MS. BROWN:

17 Q The conclusions of the Hamilton
18 article, Dr. Levy, do not support the hypothesis
19 that chronic inflammation from talcum powder
20 causes ovarian cancer. Would you agree?

21 A I would not.

22 Q The authors did not find that the
23 inflammation seen in Hamilton led to neoplastic
24 changes. True?

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1 A The authors did not report observing
2 neoplastic change over the time course of the
3 given study.

4 Q Doctor, I'm handing you the report that
5 you've served in this case, which we'll mark as
6 Exhibit 2.

7 (DEPOSITION EXHIBIT NUMBER 2
8 WAS MARKED FOR IDENTIFICATION.)

9 MS. BROWN:

10 Q And I'd like you to -- I'd like to
11 direct you to page 14. I'd like to direct your
12 attention to the last paragraph of -- the last
13 sentence -- excuse me -- of the second full
14 paragraph that begins "additional studies."

15 Do you see that sentence, Doctor?

16 A What's the beginning of that paragraph
17 so I make sure I'm looking at the right one?

18 Q Sure. I'd like to direct you on page
19 14 of your report to the second full paragraph
20 that begins "In addition to epidemiologic
21 evidence."

22 Do you see that?

23 A I do.

24 Q The last paragraph, or the last

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1 sentence of that paragraph in your report reads,
2 "Additional studies have also shown the effects
3 of talc on the immune response."

4 Do you see that sentence?

5 A I do.

6 Q And you cite the Hamilton article for
7 that proposition that we were just reviewing?

8 A Uh-huh.

9 Q True?

10 A True.

11 Q And the talc effects on the immune
12 response that were shown in Hamilton were not
13 effects that the authors observed led to
14 neoplastic changes. Correct?

15 MS. O'DELL:

16 Object to the form.

17 A I'm sorry. I'm not sure I understand
18 your question.

19 MS. BROWN:

20 Q Sure.

21 A Are you asking, if I could clarify, are
22 you -- are you asking if Hamilton is an
23 appropriate reference for the effects of talc on
24 the immune response or are you asking if

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1 Hamilton's an appropriate reference for something
2 else?

3 Q In your report, you state that studies,
4 such as Hamilton, have shown effects of talc on
5 the immune response. Correct?

6 A That is correct.

7 Q And you said Hamilton as one of the
8 articles that supports that proposition. True?

9 A Of the immune response, that's true.

10 Q Okay. The immune response that was
11 observed in Hamilton was not an immune response
12 that led to cancer. Right?

13 A As -- as I stated earlier, on the time
14 course of the Hamilton study, the authors did not
15 report specifically to neoplastic change in the
16 rat or conclude or make that conclusion, nor did
17 they conclude that that was not a possibility
18 either.

19 Q And on page 14 of your report you have
20 two additional cites for that proposition;
21 correct?

22 A Correct.

23 Q And you know, Doctor, that neither of
24 those cites, Keskin or NTP, support the

1 hypothesis that chronic inflammation leads to
2 cancer in animals. Right?

3 A The --

4 MS. O'DELL:

5 Object to the form.

6 A The -- those two references were not
7 included in the report to provide the opinion or
8 conclusions that you just described.

9 MS. BROWN:

10 Q Because you know, Doctor, that there's
11 not a single animal study that shows that talc
12 causes changes in animals that leads to cancer;
13 right?

14 MS. O'DELL:

15 Object to the form.

16 A Could you -- could you phrase that
17 question again? Sorry.

18 MS. BROWN:

19 Q There is not a single animal study,
20 Doctor, that supports the opinion that chronic
21 inflammation caused by talc causes ovarian
22 cancer. Is that correct?

23 MS. O'DELL:

24 Object to the form.

1 A In my review of the literature, there
2 are a number of animal studies that support the
3 opinions in the report regarding the biological
4 plausibility of talc leading to or contributing
5 to neoplastic change.

6 MS. BROWN:

7 Q Are you aware of any animal studies,
8 Doctor, that show talc causing chronic
9 inflammation in animals that leads to neoplastic
10 or cancerous changes in the animals?

11 MS. O'DELL:

12 Object to the form. Compound.

13 A There is one 1971 study that I'm aware
14 of. I would have to review to remember the
15 author. That was an earlier seminal -- or a
16 earlier study that described the role of talcum
17 powder and the inflammatory change within the
18 ovary.

19 MS. BROWN:

20 Q Who's the author of that study, Doctor?

21 A I'm trying to think of where I have
22 that reference.

23 Q Why don't we put that to the side and
24 at a break we'll see if we can find that article

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1 and then we can take a look at it. Okay?

2 A Uh-huh.

3 Q Okay. Getting back, then, Doctor, to
4 what we had marked as Exhibit 6, which is the
5 Taher paper, fair to say you reviewed that paper
6 after your report was submitted in this case?

7 A Yes.

8 Q Okay. And did you notice throughout
9 Taher's paper he makes reference to a number of
10 supplemental materials?

11 A Not specifically.

12 Q Are you in receipt from plaintiffs'
13 counsel of those supplemental materials?

14 A I'd have to -- you'd have to give me a
15 specific example, and I would be able to answer
16 you.

17 Q So, throughout the paper, the authors
18 make reference to a set of supplemental materials
19 that support their opinions. Do you recall that?

20 A I certainly recall the reference
21 materials to support their opinion. Whether they
22 were supplemental or otherwise, that doesn't
23 stand out to me.

24 Q Okay. And I'm not trying to be tricky.

1 I just want to know if you have those materials,
2 and, if so, I'm gonna request production of them.

3 A No. I -- I -- I don't believe that I
4 have the full list of reference -- of literature
5 cited from that -- from this paper --

6 Q Okay.

7 A -- now --

8 Q Now, Taher --

9 A -- but I'd have to check.

10 Q Sorry.

11 The Taher paper did not inform your --
12 the opinions contained in your report dated
13 November of 2018; correct?

14 A Correct, as written.

15 Q Okay. Are there any additional
16 documents that either you or your counsel have
17 brought with you here today in response to
18 Exhibit 1, the Notice of Deposition?

19 A So I'm not sure how to answer that
20 accurately, but I would say there's a -- I've
21 been provided with -- since the completion of my
22 report, I've been provided with reports from
23 other experts in the -- in the case.

24 Q Okay.

1 A And I have those on the -- available
2 electronically.

3 Q Okay. Were you provided with completed
4 versions of all the plaintiff experts in the MDL
5 proceeding?

6 A I can't speak to whether it was all,
7 but I have been provided with several.

8 Q Will you list for me the expert reports
9 you've been provided with?

10 A Sure.

11 Q Thank you.

12 A There are four on -- on this drive,
13 three -- I'm sorry. Two. Crowley and Longo.

14 Q Two reports from Dr. Crowley and two
15 reports from Dr. Longo?

16 MS. O'DELL:

17 I don't think that's what he said.

18 A No. I think there are two, two expert
19 reports, one from Dr. Crowley and one from
20 Dr. Longo.

21 MS. BROWN:

22 Q Okay. And the date of the Crowley
23 report, please?

24 A The -- according to the file, the

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1 date -- the modified date is November 28, 2018.

2 Q And --

3 A Whether that was the written date, I --
4 I don't know.

5 Q And the Longo report, do you know the
6 date of that?

7 A It is listed as August 2nd, 2017, in
8 the title. And then there's a -- sorry. There's
9 a second Longo report, 2018, which has a
10 November 28, 2018, date. So my -- my apologies.
11 To correct, there are two expert reports from
12 Dr. Longo.

13 Q Got it.

14 MS. O'DELL:

15 So when you were talking about --

16 MS. BROWN:

17 Counsel, no. Huh-uh. No. We -- I'm
18 gonna ask questions, and he's gonna answer. We
19 are not going to have you testify. You are not
20 to testify about the expert reports.

21 MS. O'DELL:

22 I'm not gonna --

23 You asked him what the date of the
24 report was.

1 MS. BROWN:

2 He -- then he will answer, counsel.

3 You can't testify.

4 MS. O'DELL:

5 He gave you the date of the file -- the

6 file date --

7 MS. BROWN:

8 That's fine.

9 MS. O'DELL:

10 -- not the date --

11 MS. BROWN:

12 On redirect, you are welcome to clean

13 up whatever you need to. But we're not gonna

14 have your testimony on the record about dates of

15 expert reports.

16 A So, looking at the report itself, the

17 date of the Longo report is November 14th, 2018.

18 MS. BROWN:

19 Q And were you provided --

20 A The -- would you like the date of the

21 earlier report?

22 Q That would be terrific.

23 A It's August 2nd, 2017.

24 Q Great.

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1 Were you provided the two Longo reports
2 and the Dr. Crowley report by plaintiffs'
3 counsel?

4 A Yes.

5 Q Do you recall when?

6 A Not specifically. It was, obviously,
7 by their date, sometime after their completion.
8 So the Crowley report and the later 2018 Longo
9 report were sometime in November or December
10 2018.

11 There's -- I've also had an opportunity
12 to review a number of -- several other expert
13 reports which are not with me today.

14 Q Do you have a listing of the additional
15 expert reports you were provided with?

16 A I'd have to -- I could certainly -- I'd
17 have to provide it. I don't, off the top of my
18 head, recall all of them. There was probably
19 approximately a dozen.

20 Q Were all of the plaintiff expert
21 reports sent to you at once?

22 MS. O'DELL:

23 Object to the form.

24 A I'm not -- I'm not certain.

1 MS. BROWN:

2 Q How did you receive them? Was it email
3 or hard copy?

4 A Neither. They were made available
5 through a shared storage.

6 Q And would you have received an email
7 alerting you to their existence on a shared file?

8 MS. O'DELL:

9 Dr. Levy, communications between
10 counsel are -- are subject to the work product
11 privilege.

12 So to the degree you're asking him to
13 convey what was in a communication, then I'll
14 object to that and instruct you not to discuss
15 communications between counsel.

16 MS. BROWN:

17 Q Which the question does not ask for,
18 Doctor.

19 MS. O'DELL:

20 I believe it does.

21 MS. BROWN:

22 Q Here's what I want to know. Did you
23 rely on any other expert reports in forming your
24 opinions in this case?

1 A To -- to my -- the content of my
2 report, no.

3 Q Did you receive the Crowley and two
4 Longo reports after you had already completed
5 your report in this case?

6 MS. O'DELL:

7 Object to the form.

8 A No. There was -- if I recall -- and
9 the -- at least the earlier Longo report -- and
10 I'd have to review the specifics -- at least the
11 earlier Longo report was reviewed and was
12 included in the content in the report.

13 And I would have to -- since the later
14 Longo report and then the final version of this
15 report were quite close together, I don't recall
16 if they overlapped or not. I'd have to review
17 the -- which references I used in here, which
18 will just take a moment.

19 So, yes, the -- I did include both
20 Longo reports.

21 Q The second Longo report was finalized
22 two days prior to your report. Is that right?

23 A Finalized, yes.

24 Q Did you see a draft of Longo's 2018

1 report?

2 A Yes. And the --

3 Q And did you --

4 A And as to when I saw the draft, I
5 believe it was -- and it was sometime in the fall
6 and/or when reports were being revised and
7 expanded as more literature became available.

8 Q Prior to Longo finalizing and signing
9 his expert report in the MDL, you had access to a
10 draft of that report; is that right?

11 MS. O'DELL:

12 Object to the form.

13 A I can't speak to -- to that accurately.

14 MS. BROWN:

15 Q I thought you just testified you saw a
16 version of the Longo 2018 report that was not
17 final. Is that correct?

18 MS. O'DELL:

19 Object to the form.

20 A I'd have to -- I'd have to review
21 my -- the -- the literature that I used for the
22 report to accurately answer your question.

23 MS. BROWN:

24 Q Well, your report doesn't say a draft,

1 and I'm wondering if you ever saw a non-finalized
2 copy of the Longo report.

3 A I didn't have an opportunity to compare
4 the finalized Longo report to a -- what may be a
5 draft or not to accurately answer your question
6 if I saw a draft that was substantially different
7 than what's referenced as the final.

8 Q There were two days between Longo
9 serving his report and you serving your report.
10 Does that help orient you as to whether you saw a
11 draft or you saw the final version?

12 A Certainly possible I saw the final
13 version.

14 Q How many hours did you spend on your
15 report in this case, Doctor?

16 A The initial draft of the report? The
17 initial writing of the report?

18 Q In total, how many hours did you spend
19 writing your report?

20 A It was 20 hours initially, and then it
21 would be -- it would be difficult to provide an
22 accurate answer for the rest of that. I would
23 say an additional few hours that I counted as
24 revision.

1 Q Did you type the expert report that
2 we've marked as Exhibit 2 yourself?

3 A I did.

4 Q Did you write all contents of Exhibit 2
5 yourself?

6 A I did.

7 Q Were there parts of your report that
8 you lifted from other published articles?

9 MS. O'DELL:

10 Object to the form.

11 A Could you describe "lifted"?

12 MS. BROWN:

13 Q Did you take the words of other authors
14 and put them in your expert report as Exhibit 2?

15 MS. O'DELL:

16 Object to the form.

17 A No. My -- my -- so my report is a
18 review of the available literature at the time
19 that the report was being developed. So, as
20 such, it describes that -- that literature.

21 As far as did I specifically copy words
22 from other reports, no.

23 MS. BROWN:

24 Q Did you work with another plaintiff

1 expert on the report that we've marked as
2 Exhibit 2?

3 A I did not.

4 Q Do you know who Dr. Zelikoff is?

5 A The name's not familiar to me.

6 Q Did you review a draft of
7 Dr. Zelikoff's report before submitting your own?

8 A I did not.

9 Q Do you think that --

10 A Not that I'm aware of.

11 Q Do you have any explanation as to why a
12 paragraph in your report is the same as a
13 paragraph in Dr. Zelikoff's report?

14 MS. O'DELL:

15 Object to the form.

16 A I -- without knowing -- without seeing
17 the paragraph in both reports would be -- I can't
18 comment.

19 MS. BROWN:

20 Q Let's mark as Exhibit 8 the expert
21 report of Dr. Judith Zelikoff, Ph.D.

22 (DEPOSITION EXHIBIT NUMBER 8

23 WAS MARKED FOR IDENTIFICATION.)

24 MS. BROWN:

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1 Q Is this something you've seen --

2 Oh, sorry. Can I --

3 It's okay, actually. It will flag it
4 for you?

5 Is this a report that you've seen
6 before, Doctor?

7 A I'll have to see it before I answer.

8 Q I'm handing you what we've marked as
9 Exhibit 8, which is the expert report of
10 Dr. Judith Zelikoff. Is this one of the reports
11 that you reviewed prior -- you reviewed at all?

12 A I would have -- I would actually have
13 to review my -- the literature that I reviewed
14 in -- the totality of the literature that I
15 reviewed, which I could answer that after a
16 break, if necessary. But I don't recall,
17 specifically recall, this report under
18 Dr. Zelikoff's name. But it is certainly
19 possible that I may have seen...

20 Q Let's look at page 5 of your report,
21 Doctor.

22 A Okay.

23 Q And why don't you put that side by side
24 with page 20 of Dr. Zelikoff's report. And the

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1 paragraph in Dr. Zelikoff's report that I want to
2 direct you to is the first full paragraph on
3 page 20 that begins "Genetic mutations."

4 Do you see that?

5 A I do.

6 Q And the paragraph of your report I want
7 to direct you to is the paragraph on page 5 that
8 begins "Both inherited."

9 Do you see that?

10 A I do.

11 Q Okay. The first sentence of that
12 paragraph in your report reads, "Both inherited
13 and acquired gene -- and acquired gene mutations
14 work together to cause cancer."

15 Do you see that?

16 A I do.

17 Q The third sentence of the paragraph I
18 directed you to in Dr. Zelikoff's report is
19 identical and reads, "Both inherited and acquired
20 gene mutations work together to cause cancer."

21 Do you see that?

22 A I do.

23 Q Those two sentences are exactly the
24 same, are they not?

1 A They are --

2 Q The next sentence --

3 A Just one moment, please. I'm just
4 making sure. Your question was are they exactly
5 the same, and I'm just confirming if they're
6 exactly the same.

7 So, yes, I agree they're exactly the
8 same.

9 Q You have reviewed them and satisfied
10 yourself that that -- those two sentences are
11 exactly the same; correct?

12 MS. O'DELL:

13 Object to the form.

14 A There's a single sentence in each
15 report that is exactly the same. But important
16 to comment that this single sentence is a -- is a
17 basic biological premise of cancer, and, so,
18 there's no surprise that two expert witnesses
19 offering opinions on the role of -- or the
20 biological plausibility or mechanisms of
21 development of cancer would introduce a
22 fundamental premise in the same manner.

23 MS. BROWN:

24 Q No surprise that you experts would have

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1 one sentence that's the same? Is that what
2 you're saying?

3 MS. O'DELL:

4 Objection. That's not what he said.
5 Misrepresents his testimony.

6 A I'm saying that both would -- both
7 reports detail a fundamental aspect as they
8 would -- based on the current understanding of
9 the -- that both inherited and acquired gene
10 mutations work in concert to cause cancer.

11 MS. BROWN:

12 Q Look at the next sentence on page 20 of
13 Dr. Zelikoff's report. It reads as follows:
14 "Even if one has inherited a genetic mutation
15 that predisposes one to cancer," comma, "that
16 doesn't mean he or she is certain to get cancer."

17 Did I read that correctly?

18 A You did.

19 Q And let's go back to page 5 of your
20 report. Skip ahead, if you would -- one, two,
21 three -- four sentences to where you were and
22 find the sentence that begins "Even."

23 Are you with me?

24 A I am.

1 Q And your report at page 5 reads, "Even
2 if one has inherited a genetic mutation that
3 predisposes one to cancer," comma, "that doesn't
4 mean he or she is certain to get cancer."

5 Did I read that correctly?

6 A You did.

7 Q That's the exact same sentence we just
8 read in Dr. Zelikoff's report; correct?

9 A It is.

10 Q So now we have two sentences that are
11 exactly the same in your report and
12 Dr. Zelikoff's report. Correct?

13 MS. O'DELL:

14 Object to the form.

15 A You have two sentences that are written
16 the same but certainly not in precisely the same
17 context or organization in the total report.

18 MS. BROWN:

19 Q We have two sentences that are
20 word-for-word identical in two of the plaintiffs'
21 expert reports in this litigation. Is that fair?

22 MS. O'DELL:

23 Objection. Asked and answered.

24 A So reading your earlier question, you

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1 asked, "Is that the same exact sentence we just
2 read in Dr. Zelikoff's report; correct?" And my
3 answer was "It is." And it remains the same.

4 Q Let's keep going.

5 Next sentence, at page 20 in
6 Dr. Zelikoff's report, states as follows:

7 "Rather," comma, "one or more additional gene
8 mutations may be needed to cause cancer."

9 Did I read that correctly?

10 A You did.

11 Q Let's go back to page 4 -- excuse me --
12 page 5 of your report where we just were. And
13 you write: "Rather," comma, "one or more
14 additional gene mutations may be needed to cause
15 cancer." Correct?

16 A Correct.

17 Q That is the identical sentence from
18 Dr. Zelikoff's report. Correct?

19 A Starting with "Rather, one or more
20 additional gene mutations may be needed to cause
21 cancer."

22 Yes, correct.

23 Q So we now have identified three
24 sentences in Dr. Zelikoff's report that are

1 identical to your report; correct?

2 A We have.

3 Q Do you have any explanation for why
4 that would be?

5 A I do.

6 Q What's that?

7 A That these -- each of these sentences
8 are describing basic introductory information
9 around the relationship between cancer and
10 genetic mutation.

11 Q And each of you described it with the
12 exact same words?

13 A Apparently so.

14 Q Let's keep going.

15 Page 20 of Dr. Zelikoff's report,
16 picking up where we left off, Dr. Zelikoff
17 writes: "The inherited gene mutation could
18 instead make one more likely to develop cancer
19 when exposed to certain cancer-causing
20 substances."

21 Do you see that?

22 A I do.

23 Q And let's go back to where we were in
24 your report, on page 5. "The inherited gene

1 mutation could instead make one more likely to
2 develop cancer when exposed to a certain
3 cancer-causing substance."

4 Do you see that?

5 A I do.

6 Q And other than the tense in that last
7 sentence, they, too, are identical. Correct?

8 A So they're -- they're certainly similar
9 sentences, but that -- I believe the tense is an
10 important difference between them.

11 Again, as I stated, that these are
12 introductory and fundamental perspectives on
13 cancer and that, in this case, two expert
14 witnesses have summarized those things in a
15 similar fashion.

16 Q It doesn't strike you as odd that four
17 sentences are identical from two expert reports?

18 MS. O'DELL:

19 Object to the form.

20 A Four sentences are not identical.

21 MS. BROWN:

22 Q There's one small change in a tense.
23 That's it. Right, Doctor?

24 MS. O'DELL:

1 Object to the form.

2 A There -- there are -- there are three
3 sentences which are, when considered
4 individually, they are the same words. When you
5 consider the -- now the group of those four
6 sentences together between the two reports, they
7 are clearly different organization with
8 significantly more information between those
9 identical sentences in one or the other.

10 So the suggestion that they were -- one
11 report was copied into the other, I would say it
12 is equally interesting that they are more
13 different than they are alike, other than the
14 wording of three sentences.

15 MS. BROWN:

16 Q Did someone other than you write the
17 sentences we've just been looking at in your
18 report?

19 A No.

20 Q Did you consult the Mayo Clinic's
21 website in connection with writing your report?

22 A I don't believe so.

23 Q Do you consider the Mayo Clinic's
24 website to be authoritative -- an authoritative

1 source, in your view?

2 MS. O'DELL:

3 Object to the form.

4 A I have no basis for that opinion. I --

5 I haven't reviewed the Mayo Clinic website to

6 determine that.

7 (DEPOSITION EXHIBIT NUMBER 9

8 WAS MARKED FOR IDENTIFICATION.)

9 MS. BROWN:

10 Q Handing you, Doctor, what we've marked

11 as Exhibit 9 to your deposition, which is a

12 printout from the Mayo Clinic website entitled

13 "Cancer."

14 A Uh-huh.

15 Q I'll hand it to you. And let me know

16 if this is something that you've ever seen

17 before.

18 A Not that I recall.

19 Q Did you take any language from the Mayo

20 Clinic website to use in your report?

21 A No.

22 Q Let's take a -- I want you to put the

23 Mayo Clinic, which we've marked as Exhibit 9 --

24 A Uh-huh.

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1 Q -- next to your report, which remains
2 Exhibit 2. And I will direct you to the second
3 page of the Mayo Clinic printout, the section
4 titled "Causes."

5 Are you with me?

6 A Second page.

7 Q Double-sided. Flip it over.

8 A Yes.

9 Q Okay. And I'll direct you to page 3 of
10 your report entitled "The Role of Gene Mutations
11 in the Development of Cancer."

12 A Uh-huh.

13 Q Starting with Exhibit 9, the Mayo
14 Clinic website, under a section entitled
15 "Causes," the Mayo Clinic writes, "Cancer is
16 caused by changes" -- parentheses --
17 "(mutations) to the DNA within cells."

18 Do you see that?

19 A I do.

20 Q And, looking at page 3 of your report,
21 Doctor, that same sentence or sentence fragment
22 appears in the first sentence: "Cancer is caused
23 by changes" -- parentheses -- "(mutations) to the
24 DNA within cells."

1 Correct?

2 MS. O'DELL:

3 Object to the form.

4 A Say your question again. Are you
5 asking --

6 MS. BROWN:

7 Q It's the same; right, Doctor?

8 MS. O'DELL:

9 Object to the form.

10 A There are eight words or ten words that
11 are the same in this first sentence, again, both
12 describing some of the fundamental premise of
13 cancer and its -- in its description.

14 MS. BROWN:

15 Q Let's go to the second sentence in the
16 Mayo Clinic website, which reads, "The DNA inside
17 a cell is packaged into a large number of
18 individual genes, each of which contains a set of
19 instructions telling the cell what functions to
20 perform," comma, "as well as how to grow and
21 divide."

22 Do you see that?

23 A I do.

24 Q And a nearly identical version of that

1 sentence appears in your report at page 3 where
2 you state, "The DNA that makes up our genetic
3 code is organized into a large number of
4 individual genes, each of which contains a
5 specific subset of instructions telling the cell
6 what functions to perform," comma, "as well as
7 how to grow and divide."

8 Do you see that?

9 A I do.

10 Q Do you notice that nearly all the words
11 are the same as the Mayo Clinic's?

12 MS. O'DELL:

13 Objection to form.

14 A I, again -- we -- we have another
15 example of similar language describing
16 introductory and fundamental aspects surrounding
17 the basics of cancer biology.

18 MS. BROWN:

19 Q Back to the Mayo Clinic next sentence.

20 Quote: "Errors in the instructions can cause the
21 cell to stop its normal function and may allow a
22 cell to become cancerous."

23 Do you see that?

24 A I do.

1 Q Back to your report at page 3. An
2 identical sentence: "Errors in the instruction
3 can cause the cell to stop its normal function
4 and may allow a cell to become cancerous."

5 Do you see that?

6 A I do.

7 Q Does that strike you as strange?

8 MS. O'DELL:

9 Object to the form.

10 A Strange in what way?

11 MS. BROWN:

12 Q That your expert report in this
13 litigation contains identical sentences to the
14 Mayo Clinic's website.

15 MS. O'DELL:

16 Objection. Misstates the report.

17 A I -- I don't find it surprising in the
18 least.

19 MS. BROWN:

20 Q Let's turn to page 4 of your report,
21 please. And I'll direct you to the final bullet
22 on the same page of the Mayo Clinic website you
23 were just looking at. The section of your report
24 on page 4 I'd like to direct you to is the

1 subparagraph titled "Loss of DNA Repair."

2 Are you with me?

3 A Yes.

4 Q I'm gonna read you two sentences from
5 the Mayo Clinic. Tell me if I read them
6 correctly.

7 "DNA repair genes look for errors in a
8 cell's DNA and make corrections. A mutation in a
9 DNA repair gene may mean that other errors aren't
10 corrected, leading cells to become cancerous."

11 Do you see those two sentences, Doctor?

12 A I do.

13 Q Those are two sentences written by the
14 folks who produce the Mayo Clinic's website;
15 correct?

16 A I -- I have no knowledge of who wrote
17 that.

18 Q The same two sentences appear in your
19 report on page 4. Quote: "DNA repair genes look
20 for errors in a cell's DNA and make corrections.
21 A mutation in a DNA repair gene may mean that
22 other errors aren't corrected, leading cells to
23 become cancerous."

24 Do you see that?

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1 A I do.

2 Q Those two sentences are identical in
3 the Mayo Clinic's website and your report. True?

4 MS. O'DELL:

5 Object to the form.

6 A Again, we have fund- -- basic
7 information that provides an introductory
8 description of the basics of cancer which is used
9 as -- as an inform- -- informatory foundation for
10 latter opinions in the report but is not germane
11 to the -- to the opinion in my report.

12 And, again, as stated before, that
13 succinct fundamental information regarding cancer
14 biology in two sources that state things
15 succinctly and clearly in layman's language
16 are -- are similar or even identical, again, does
17 not surprise me.

18 MS. BROWN:

19 Q We read at least four sentences that
20 are identical to the Mayo Clinic. Would you
21 agree?

22 MS. O'DELL:

23 Objection to form. The sentences are
24 not identical.

1 MS. BROWN:

2 Counsel, form.

3 A There are some similar -- there are
4 some similarly stated sentences that
5 you're -- that you've taken out of context in
6 both cases to find them identical. So I -- I
7 agree that they're identical, but, again,
8 don't -- don't necessarily am surprised since I
9 have no knowledge of where the information from
10 the Mayo website was taken from.

11 MS. BROWN:

12 Q You agree a number of sentences in your
13 report are identical to a number of sentences on
14 the Mayo Clinic's website. True?

15 MS. O'DELL:

16 Object to the form.

17 A No. I agree that they're -- I don't
18 agree. There are specific wordings that are the
19 same.

20 MS. BROWN:

21 Q Doctor, do you not agree that a number
22 of the sentences we just read are identical to a
23 number of sentences that appear on the Mayo
24 Clinic's website?

1 MS. O'DELL:

2 Object to the form.

3 A I think we've -- we've specifically
4 gone over those individually and answered those
5 questions.

6 MS. BROWN:

7 Q And you'll agree the sentences are
8 identical?

9 MS. O'DELL:

10 Object to the form.

11 A Again, I -- I've answered -- I've
12 answered those when we went through them
13 individually.

14 MS. BROWN:

15 Q Well, I want you to answer my question
16 now.

17 You'll agree we've looked at a number
18 of sentences that are identical in your report to
19 the information on the Mayo Clinic's website;
20 correct?

21 MS. O'DELL:

22 Object to the form. Misstates his
23 testimony.

24 A I'd have to go back to the transcript

1 from our conversation to comment on those.

2 MS. BROWN:

3 Q You have it right in front of you. We
4 just looked at them.

5 A We did.

6 Q Right?

7 A Yes.

8 Q You recall reading a number of
9 sentences in the Mayo Clinic website that match
10 word for word a number of sentences in your
11 report. True?

12 MS. O'DELL:

13 Object to the form.

14 A We've -- we've read information that
15 is -- that is similar between the two documents.
16 And, as answered, given the, again, basic
17 fundamental introduction in lay language for
18 these concepts, it is no surprise that it's the
19 same.

20 MS. BROWN:

21 Q You're not surprised to find identical
22 sentences in your report and Dr. Zelikoff's
23 report?

24 A I'm not surprised.

1 MS. O'DELL:

2 Object to the form.

3 MS. BROWN:

4 Q You are not surprised to find identical
5 sentences in your report and the Mayo Clinic?

6 MS. O'DELL:

7 Objection to form. Asked and answered.

8 A No. I -- I've answered that.

9 MS. BROWN:

10 Q You need to answer it again.

11 Are you --

12 A I'm not surprised.

13 Q -- surprised?

14 Did you consult Wikipedia in writing
15 your expert report?

16 A I don't recall.

17 Q Do you think it's possible you might
18 have looked at Wikipedia when writing your expert
19 report in this litigation?

20 A I've -- I've looked -- I've looked at a
21 large number of sources in published literature
22 and others.

23 Q Did one of those sources include
24 Wikipedia?

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1 A I don't recall.

2 Q Do you consider Wikipedia to be a
3 scientifically reliable source?

4 A What do you mean by scientifically
5 reliable.

6 Q Do you understand the concept of
7 scientific reliability when answering a
8 scientific question?

9 MS. O'DELL:

10 Object to the form.

11 A Again, you'd have to -- that's -- you'd
12 have to explain your -- what scientific
13 reliability means in the context of your
14 question.

15 MS. BROWN:

16 Q What does it mean to you?

17 A Scientific reliability? In general
18 terms, it would mean information that comes from
19 a peer-reviewed source.

20 Q And Wikipedia is not peer-reviewed;
21 correct?

22 A Wikipedia generally reso- -- uses
23 a -- is a summary of commonly -- at least in
24 scientific terms, a number of peer-reviewed

1 sources, but it is --

2 So from a true peer-review perspective,
3 Wikipedia actually is peer-reviewed in the sense
4 that anyone can contribute and edit the
5 information in Wikipedia.

6 Q Including our kids; right?

7 MS. O'DELL:

8 Object to the form.

9 A Possible.

10 MS. BROWN:

11 Q Anyone in the world could edit a
12 Wikipedia page. True?

13 A I believe so.

14 Q Is it your testimony, Doctor, that
15 information from Wikipedia is a reliable resource
16 when answering a scientific question?

17 A No, that is not my testimony. That is
18 not my testimony, no.

19 Q Do you -- do you think you used
20 Wikipedia here in writing your report?

21 A Again, I -- I -- I don't recall using
22 Wikipedia specifically.

23 Q Okay. Let's take a look at your report
24 at page 7, Doctor.

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1 And we'll mark a Wikipedia page as
2 Exhibit 10.

3 (DEPOSITION EXHIBIT NUMBER 10
4 WAS MARKED FOR IDENTIFICATION.)

5 MS. BROWN:

6 Q I would like to direct you, Dr. Levy,
7 to the first full paragraph in your expert report
8 at page 7.

9 A Uh-huh.

10 Q Do you see that?

11 A I do.

12 Q And I want to direct your attention to
13 the sentence in the middle of that paragraph that
14 begins "BRCA1 combined."

15 Do you see that?

16 A Yes.

17 MS. BROWN:

18 Q And I want to, side by side with
19 Wikipedia, direct your attention to the third
20 full paragraph that begins, as well, "BRCA1
21 combined."

22 You with me?

23 A I am.

24 Q Wikipedia writes, "BRCA1 combines with

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1 other tumor suppressors, DNA damage sensors, and
2 single transducers to form a large multi-subunit
3 protein complex known as BRCA1-associated genome
4 surveillance complex" -- parens --

5 "BAC-" -- excuse me -- "(BASC)," end parens.

6 Do you see that?

7 A I do.

8 Q Turning to your report, page 7, you
9 write, "BRCA1 combines with other tumor
10 suppressors," comma, "DNA damage sensors, and
11 signal transducers to form a large multi-subunit
12 protein complex known as the BRCA1-associated
13 genome surveillance complex" -- parens --
14 (BASC)."

15 Correct?

16 A That is correct.

17 Q Those two sentences, Doctor, are
18 identical.

19 A It appears so, yes.

20 Q Okay.

21 A Except for a -- the reference included
22 on the Wikipedia page is not included in my
23 report.

24 Q Wikipedia has cited a reference, and

1 your sentence stands without a reference. Is
2 that right?

3 A That's right.

4 Q Other than the footnote, the two
5 sentences we just read are identical. True?

6 A Both sentences state the same fact in
7 the same way. So, similar to our earlier
8 discussions, we've now seen a large collection of
9 fundamental factual information with -- with
10 accurate information from now a number of sources
11 that are stated in similar ways through
12 Wikipedia, other expert reports, and websites all
13 about the fundamentals of cancer.

14 Q The two sentences we just read, Doctor,
15 are identical. Correct?

16 MS. O'DELL:

17 Object to the form.

18 A We read one sentence in Wikipedia.

19 MS. BROWN:

20 Q And it is identical. True?

21 A Yes. The wording is the same. With,
22 of course, Wikipedia, as you already stated,
23 being editable by anybody and can pull that
24 content from anywhere, and it's the -- I'd have

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1 to review -- I'd have to look to see what
2 reference 16 in Wikipedia is. But it's certainly
3 possible that I and Wikipedia summarized the same
4 information from the same source.

5 Q Let's go to page 9 of your report. One
6 of the articles that you relied on is an article
7 by Lisa Coussens and Zena Werb. Do you recall
8 that?

9 A That does sound familiar, but I'll have
10 to verify.

11 Q Handing you what we've marked as
12 Exhibit 12 [sic] to your report, the Coussens and
13 Werb article.

14 (DEPOSITION EXHIBIT NUMBER 11
15 WAS MARKED FOR IDENTIFICATION.)

16 A Yes, this is a -- this is a review.
17 This is an insight review article, which, similar
18 to my report, is likely consolidating information
19 from the research knowledge.

20 MS. BROWN:

21 Q I'd like to direct you to the last two
22 sentences of Exhibit 10, the Coussens' article,
23 the last two sentences in the first paragraph.

24 A Exhibit 10 or 12?

1 Q I'm sorry. What did we mark the
2 Coussens as? 12?

3 A Twelve.

4 Q That should have been 11.

5 We have marked the Coussens' article
6 now correctly as Exhibit 11, and I'll direct you
7 to the last two sentences of the first full
8 paragraph. Put that, if you would, Doctor, side
9 by side with your report at page 9, sentence that
10 begins "in contrast," both sentences that begin
11 "in contrast."

12 Are you with me?

13 A I am.

14 Q All right. So, in this published
15 article, Ms. or Dr. Coussens writes, "In
16 contrast, proliferating cells that sustain
17 DNA" --

18 MS. O'DELL:

19 Excuse me, Alli. Sorry. Tell me, are
20 you in the second paragraph?

21 MS. BROWN:

22 I'm on the end of the first full
23 paragraph.

24 MS. O'DELL:

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1 Sorry. I thought you were in the first
2 full paragraph.

3 MS. BROWN:

4 Begins "In contrast."

5 MS. O'DELL:

6 Okay.

7 MS. BROWN:

8 And we have that side by side with
9 Dr. Levy's report, page 9, the paragraph that
10 also begins "In contrast."

11 MS. O'DELL:

12 Thank you.

13 MS. BROWN:

14 Q Dr. Coussens writes, "In contrast,
15 proliferating cells that sustain DNA damage
16 and/or mutagenic assault" -- parens -- "(for
17 example, initiated cells), continue to
18 proliferate in microenvironments rich in
19 inflammatory cells and growth/survival factors
20 that support their growth."

21 Do you see that sentence?

22 A I do.

23 Q The next sentence reads, "In a sense,"
24 comma, "tumors act as wounds that fail to heal."

1 See that?

2 A I do.

3 Q Directing your attention to page 9 of
4 your report, Doctor, you write, "In contrast,"
5 comma, "proliferating cells that sustain DNA
6 damage and/or mutagenic insult -- parens -- "(for
7 example," comma, "initiated cells)," end paren,
8 "continue to proliferate in microenvironments
9 rich in inflammatory cells and growth/survival
10 factors that support their growth," period. "In
11 a sense, tumors act as wounds that fail to heal."

12 Do you see that?

13 A I do.

14 Q Except for one word, Doctor, those two
15 sentences, including the slashes and the
16 parentheses, are identical. Correct?

17 MS. O'DELL:

18 Object to the form.

19 A Those two sentences are similar.

20 MS. BROWN:

21 Q Except for one word, those two
22 sentences are identical. True?

23 MS. O'DELL:

24 Object to the form. Asked and

1 answered.

2 A Yeah. I'd certainly appreciate the
3 similarity between the -- between the two. But
4 that's -- again, as we've been discussing now for
5 an extensive amount of time, in the introductory
6 review content of the report --

7 In fact, I reference the Coussens and
8 Werb paper, so certainly it's not a surprise that
9 wording is similar between them and used similar
10 language to describe, again, these factual
11 aspects of fundamental cancer biology, including
12 similar references.

13 MS. O'DELL:

14 Excuse me. My microphone is broken.

15 VIDEOGRAPHER:

16 It's still working. You're good. You
17 can just lay it on the table and we'll fix it at
18 a break.

19 MS. O'DELL:

20 And we've been going about an hour and
21 13 minutes.

22 MS. BROWN:

23 I'm about to finish up this section.
24 We'll take a break.

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1 Q My question, Doctor, was: Except for
2 one word, the two sentences we just read from
3 Coussens are identical to the two sentences in
4 your report. Is that correct?

5 MS. O'DELL:

6 Object to the form.

7 A So, I -- as -- as stated, the two
8 sentences are similar.

9 MS. BROWN:

10 Q Except for one word, they are
11 identical. Is that correct?

12 MS. O'DELL:

13 Object to the form. He's asked --
14 you've asked the question. He's answered your
15 question.

16 A Again, the two sentences are similar.

17 MS. BROWN:

18 Q Do you understand "identical," what
19 "identical" means?

20 A Yes. Exactly the same.

21 Q Okay. Except for one word, those two
22 sentences are exactly the same in the Coussens
23 article and your report. True?

24 MS. O'DELL:

1 Object to the form. Asked and
2 answered.

3 A And we're -- we're saying the same
4 thing in different ways, which is that the two
5 sentences are similar, stating factual
6 information about fundamental cancer biology and
7 in two similar review articles.

8 MS. BROWN:

9 Q And the only difference is one word.
10 Correct?

11 A Two sentences are similar.

12 Q My question was: The only difference
13 is one word. True?

14 A Let me review again to be sure that we
15 would -- before answering.

16 Taken out of context, those two
17 sentences are similar.

18 Q My question was, Doctor, the only
19 difference is one word. Is that correct?

20 MS. O'DELL:

21 Objection to the form. Asked and
22 answered.

23 A You know, I think we've -- we've
24 answered this a number of times, that the two

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1 sentences are different in their context and in
2 terms of paragraph, but they are similar in
3 structure and similar in wording.

4 But, as you stated, with the exception
5 of the -- so they're not. So in a language
6 perspective, they're not identical. They're
7 similar.

8 MS. BROWN:

9 Let's take a break.

10 VIDEOGRAPHER:

11 Going off -- going off the record. The
12 time is 10:15 a.m.

13 (OFF THE RECORD.)

14 VIDEOGRAPHER:

15 We're back on the record. The time is
16 10:25 a.m.

17 MS. BROWN:

18 Q Doctor, I am handing you what I have
19 marked as Deposition Exhibit 12 and 13. These
20 are additional documents your counsel identified
21 for us this morning as something you have seen
22 since your report.

23 (DEPOSITION EXHIBITS 12 AND 13

24 WERE MARKED FOR IDENTIFICATION.)

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1 MS. BROWN:

2 Q Would you tell us what those two
3 exhibits are, please.

4 A Exhibit -- Exhibit 13 is a printed copy
5 of an email dated December 26th informing
6 Dr. Saed that a manuscript --

7 Is it helpful to identify the
8 manuscript?

9 -- titled "Molecular Basis Supporting
10 the Association of Talcum Powder Use With
11 Increased Risk of Ovarian Cancer," submitted to
12 Reproductive Sciences, has been reviewed. The
13 comments were included in the letter.

14 Q Have you seen --

15 A And I'm just reading the --

16 Q Sure.

17 A It -- it appears that the -- so,
18 summarizing the letter, the manuscript has been
19 reviewed, the comments from the reviewers were
20 provided back, and the journal has informed
21 Dr. Saed that they'll accept a revised document
22 for potential publication.

23 Q Have you seen Exhibit 13 prior to this
24 morning?

1 A I have.

2 Q Have you seen the reviewer comments
3 referenced in Exhibit 13?

4 A I have not seen the reviewer comments.

5 Q Okay. Exhibit 13 does not inform the
6 opinions of your report dated November of 2018.
7 True?

8 A Exhibit 13, being the letter, that is
9 correct. It does not.

10 Q Okay. And what's Exhibit 12?

11 A Exhibit 12 appears to be a preprint
12 version of the previously mentioned paper,
13 "Molecular Basis Supporting the Association of
14 Talcum Powder Use With Increased Risk of Ovarian
15 Cancer," with the first author, Nicole Fletcher,
16 and Dr. Saed is listed as the senior or
17 corresponding author.

18 Q Did the lawyers provide you with this
19 manuscript, Doctor?

20 A Yes, in a -- but that's -- yes, they
21 did.

22 Q Do you recall when you were provided
23 with a copy of the manuscript by the plaintiffs'
24 lawyers?

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1 A It was sometime in December toward --
2 late in the year. The exact date, I'd have to
3 review when it came in. And I believe it was --
4 and the version you have here is a more formal
5 preprint version from the -- from Manuscript
6 Central, whereas the version I received
7 was a -- it appeared to be more of a submission
8 version.

9 So commenting whether it's
10 exact -- precisely the same content, I -- I
11 wouldn't be able to say.

12 Q Fair to say, though, Doctor, since you
13 received the manuscript in December of 2018, the
14 contents of the manuscript did not inform the
15 expert report that you wrote in November of 2018;
16 correct?

17 A Actually, I would say the -- the -- I
18 would not agree, from the perspective of Dr. Saed
19 has a number of similar studies, as well as a
20 number of abstracts that I had the opportunity to
21 review that did inform some of the opinions in
22 the report. Those same information and data were
23 included in this manuscript and expanded upon
24 actually significantly.

1 So the basis of my opinion includes
2 some of the information from this manuscript, but
3 I -- but the report does not contain the totality
4 of this.

5 Q Right. Because the manuscript wasn't
6 available to you until after you wrote your
7 report. Right?

8 A No, that's not the case. The -- the --
9 the research, some of the research information
10 from this study was available in abstract form,
11 and -- and some -- I believe a preprint from
12 Dr. Saed.

13 So it was -- so it was available.
14 Portions of it were available for the report.

15 Q Other than the abstract, did you have
16 access to an earlier version of what we've marked
17 as Exhibit 12?

18 A I can't accurately answer that without
19 comparing them.

20 Q Where do you have stored the earlier
21 version that you're referring to?

22 A Let's see if I -- what I have here.

23 So, from Dr. Saed, I have a -- used a
24 book chapter which describes some of his

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1 oxidative stress experiments that are also
2 consistent with the information that's in the --
3 in Exhibit 12, as well as some of his earlier
4 review articles, and that's --

5 Let me make sure I'm not missing
6 anything from Fletcher, who's been...

7 But, otherwise, the -- the experiments
8 that were expanded upon in the formal manuscript
9 were described in -- in abstract or, I should
10 say, summarized form, meaning an abstract that
11 included methods, results, and conclusions from
12 Fletcher and colleagues in Dr. Saed's group.

13 Q At the time you wrote your report, you
14 had an abstract of the 2018 paper that we've
15 marked as Exhibit 12; correct?

16 MS. O'DELL:

17 Object to the form. He said plural.

18 A Yes. I had two abstracts and then
19 possibly --

20 I'd have to review when I received this
21 preprint versus the final version of my report to
22 see if they overlapped, if they're -- if I had an
23 opportunity to review this or not.

24 MS. BROWN:

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1 Q Okay. And I'll ask if you'd be kind
2 enough to do that at a break. Just let us know
3 if you had access to something other than the
4 abstract of Dr. Saed's 2018 report at the time
5 you wrote your report. Fair enough?

6 A I'll make a note.

7 MS. O'DELL:

8 Excuse me. Object to the form.

9 Abstracts, not one.

10 MS. BROWN:

11 Q Dr. Levy, you are a Ph.D.; is that
12 correct?

13 A Correct.

14 Q Okay. You are not an M.D.; correct?

15 A That's correct.

16 Q What's your Ph.D. in, sir?

17 A Biochemistry and genetics.

18 Q You're not an epidemiologist. Fair?

19 A I am not.

20 Q Okay. And the focus of your work at
21 HudsonAlpha is on genome sequencing. Is that
22 right?

23 A No. The -- the -- genome sequencing is
24 a tool that we apply in -- in the work of my

1 laboratory and in my responsibilities at
2 HudsonAlpha.

3 Q HudsonAlpha has a team known as the
4 Breakthrough Breast and Ovarian Cancer Team. Is
5 that right?

6 A I'm not familiar with that name.

7 Q Okay.

8 A There is a -- a group of faculty who
9 have some funding related to breast and ovarian
10 cancer. It's -- it's certainly possible that
11 name was used in -- in press for some title.

12 Q Since you're not familiar with that
13 team, fair to say you're not a member of the
14 Breakthrough Breast and Ovarian Cancer Team?

15 MS. O'DELL:

16 Object to the form.

17 A Again, I don't -- my involvement with
18 breast and ovarian cancer at HudsonAlpha is
19 specific to some projects. And whether or not I
20 was named on that team, I -- I don't know.

21 MS. BROWN:

22 Q There are folks at HudsonAlpha,
23 scientists and doctors at HudsonAlpha whose
24 practice is devoted to studying ovarian cancer.

1 Correct?

2 A No, that's not correct.

3 Q Your practice is not devoted to ovarian
4 cancer; correct?

5 MS. O'DELL:

6 Object to the form.

7 A No. My -- my practice is not devoted
8 to ovarian cancer. And -- but that was
9 irrelevant to what I was asked to do in
10 this -- in this particular case for
11 the -- regarding the content of my report.

12 MS. BROWN:

13 Q I think I saw you've published one
14 article regarding ovarian cancer over the course
15 of your career. Is that right?

16 A That sounds correct.

17 Q You have not given any presentations
18 regarding ovarian cancer. Is that true?

19 A I would say that's accurate.

20 Q You have not received any government
21 funding to study ovarian cancer. True?

22 A I received government funding to study
23 breast and ovarian cancer -- this was in 2002,
24 from the Department of Defense -- and then,

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1 subsequent to that, participated in at least one
2 review for the Department of Defense in reviewing
3 ovarian cancer research grants. So that is --

4 And then my membership in the
5 Vanderbilt Cancer Center as well as the
6 University of Alabama Birmingham Comprehensive
7 Cancer Center certainly have been involved in a
8 number of projects across a diversity of cancer
9 types, including ovarian and breast cancer.

10 Q Prior to being hired by the plaintiffs'
11 lawyers in this litigation, you had not
12 investigated the potential mechanisms by which
13 talcum powder could cause ovarian cancer. Is
14 that fair?

15 MS. O'DELL:

16 Object to the form.

17 A Specific -- as in terms of a specific
18 fundamental research project?

19 MS. BROWN:

20 Q At all.

21 MS. O'DELL:

22 Object to the form.

23 A So my research has included the role of
24 inflammation and a number of biological processes

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1 dating back to my early Ph.D. work, and those
2 include cancer. So certainly the subject of
3 inflammatory response in -- both chronic and
4 acute, in controlling cancer has been a subject
5 of my research for some time and certainly
6 bridged into ovarian cancer as well as other
7 cancer types.

8 MS. BROWN:

9 Q You've never published on chronic
10 inflammation as a potential mechanism by which
11 talcum powder causes ovarian cancer. Correct?

12 A Not specific to talcum powder, no.

13 Q You have never given a presentation on
14 chronic inflammation as a mechanism for causing
15 ovarian cancer at all; right?

16 MS. O'DELL:

17 Object to the form.

18 A I'm thinking through my --

19 I don't recall a specific presentation
20 with regards to talcum powder and its role in
21 ovarian cancer. As far as my discussions or
22 presentations around the role of inflammation in
23 cancer, including ovarian, it -- it is -- it is
24 possible, but I can't think of a specific

1 presentation.

2 MS. BROWN:

3 Q Okay. Since you've been hired by
4 plaintiffs' lawyers, you have done some research
5 into the potential role of inflammation and
6 ovarian cancer. Is that right?

7 MS. O'DELL:

8 Object to the form.

9 A Since -- since my -- what was requested
10 of me from the plaintiffs' attorneys was to
11 provide a review of the biological plausibility
12 and a connection between talcum powder and
13 inflammation and then discuss the relationship
14 between inflammation and cancer.

15 MS. BROWN:

16 Q Okay. As I understand you, Dr. Levy,
17 you were asked by the plaintiffs' lawyers to
18 provide a review of the literature as it relates
19 to the biological plausibility of talcum powder
20 and ovarian cancer. Is that right?

21 MS. O'DELL:

22 Object to the form.

23 A No, that's not correct. What I was --
24 I was asked to provide an opin- -- expert opinion

1 on the biological plausibility of the mechanism
2 that -- of the ability of exposure of talc and
3 its constituent components to cause inflammation
4 and/or cancer.

5 MS. BROWN:

6 Q Do you see those as two different
7 things?

8 A Yes.

9 Q Okay. So you were asked to provide a
10 mechanism by which talcum powder could cause
11 cancer?

12 A No, that's not correct.

13 MS. O'DELL:

14 Objection to form.

15 MS. BROWN:

16 Q Okay. Explain it to me.

17 A I -- I was asked to provide a -- an
18 opinion on the biological plausibility --

19 Q Of talcum powder causing cancer?

20 A -- of talcum powder leading to the
21 biological changes necessary to cause cancer.

22 Q Okay. As I understand what you just
23 said, you were asked to re- -- to provide an
24 opinion on the biological plausibility of talcum

1 powder leading to biologic changes that are
2 needed to cause cancer. Is that fair?

3 MS. O'DELL:

4 Object to the form.

5 A So I was asked from -- by the attorneys
6 to review the available literature across the
7 spectrum of cancer and talcum powder and
8 constituent literature to develop an opinion
9 around the biological plausibility that exposure
10 of -- exposure to talcum powder is
11 biologically -- that there is a biologically
12 plausible mechanism that that can cause cancer.

13 MS. BROWN:

14 Q Okay. And that is not something that
15 you had done prior to being hired by the
16 plaintiffs' lawyers. Fair?

17 A Developing such an opinion?

18 Q Correct.

19 A Or -- or -- so writing such a report,
20 no, that is not something I -- I had done prior
21 to -- to this. My research has been primarily in
22 data integration and the examination of
23 mechanistic effects in cancer, rare disease,
24 and -- and in diabetes specifically, as well as

1 some neurological diseases.

2 So this was a similar review as -- of
3 those topics when asked to examine the biological
4 plausibility of a cause and effect; in this case,
5 cause being exposure to talcum powder and effect
6 being progression to cancer.

7 Q Prior to being hired by the plaintiffs'
8 lawyers, you had not considered the biological
9 plausibility of talcum powder causing ovarian
10 cancer. Correct?

11 A No. I would say that's not true in
12 isolation. And the reason I say that's not true
13 is I had been aware of some of the literature and
14 certainly some of the press that surrounded the
15 suspected associations between talcum powder
16 exposure and cancer. So I was familiar with the
17 concept, but I had not at the time, until hired
18 by the plaintiffs' attorney, spent a significant
19 amount of time reviewing the literature and
20 developing a written opinion as to that
21 biological plausibility.

22 Q You have not published your opinion
23 contained in -- your opinions contained in the
24 report that we marked as Exhibit 2. Is that

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1 correct?

2 A That is correct.

3 Q You have not presented the opinions
4 contained in Exhibit 2 at any medical or
5 scientific conference; correct?

6 A That's correct.

7 Q You have not disclosed the opinions
8 contained in Exhibit 2 to any of your colleagues;
9 correct?

10 MS. O'DELL:

11 Object to the form.

12 A Not at this time, no. Considering I
13 had -- I had just finalized the report a short
14 time ago, I haven't had the opportunity to
15 consider publication, presentation, or -- or
16 discussion with colleagues.

17 MS. BROWN:

18 Q Do you plan to seek publication of the
19 information contained in your report in Exhibit
20 2?

21 A I -- I haven't made a determination at
22 this time. It's been a fascinating area to
23 research. Certainly there's -- that would
24 certainly be a future possibility.

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1 Q Does HudsonAlpha --

2 First of all, what's your position at
3 HudsonAlpha, Doctor?

4 A So I'm a faculty investigator, which
5 would be analogous to a faculty member at a
6 research institution, similar to -- or I should
7 take a step back and just --

8 To be accurate, HudsonAlpha is a
9 private nonprofit research institution, similar
10 to Broad Institute, Stowers, et cetera. So we
11 are academic in nature, meaning that most of our
12 funding or the vast majority of our funding comes
13 from grants and contracts. So that's why I say
14 it's analogous to faculty at a research
15 institution.

16 My other responsibilities are the
17 management and oversight of the production and
18 research laboratories, so that provides us an
19 opportunity to work with approximately 1200
20 different laboratories from around the world in
21 support of roughly 5,000 projects over the last
22 nine and a half years. And that's -- it's
23 provided a broad spectrum of activities and
24 abilities to work in these types of projects.

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1 And then I also oversee the clinical
2 laboratories as well. And adult oncology is a
3 major focus of that research. I currently lead
4 the largest profiling effort in adult cancer in
5 the nation, which involves 15 national cancer
6 institutes. And ovarian cancer is a component of
7 that research, although not the only cancer that
8 we research in that -- in that's -- in that
9 program.

10 Q None of the 5,000 projects you just
11 mentioned have dealt with talc. Is that fair?

12 A That is fair.

13 Q And none of the work at the clinical
14 labs that you just mentioned have dealt with
15 talc; correct?

16 MS. O'DELL:

17 Object.

18 A I am -- I would say there's a
19 statistical probability that some of the ovarian
20 cancer samples that have been observed in the
21 clinical laboratory may very well have
22 been -- have come from patients exposed to talcum
23 powder. But I have no direct knowledge of that,
24 nor have we performed any testing to confirm

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1 or -- or -- or dispute whether or not those
2 ovarian cancer or other cancer types may have had
3 a relationship to talcum powder. So the short
4 answer being I -- I don't have the information to
5 answer that.

6 MS. BROWN:

7 Q HudsonAlpha has a Code of Ethics. Are
8 you familiar with it?

9 A Yes.

10 Q Are you familiar with the financial
11 disclosure requirements of HudsonAlpha?

12 A I am.

13 Q Have you complied with those in
14 connection with your work as an expert witness
15 for plaintiffs in this case?

16 A I have.

17 Q And tell us what you've done to comply
18 with HudsonAlpha's Code of Ethics and financial
19 disclosure requirements.

20 A Their Code of Ethics and financial
21 requirement is requirement to disclose any
22 relationships that have a financial component
23 over -- I don't recall the minimum amount, but it
24 is -- it is fairly modest, hundreds of dollars.

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1 And that reporting requirement is the -- is -- is
2 for the previous year, and it is due in July, I
3 believe is the time frame, although I'd have to
4 make sure. It's -- I know it's not the end of
5 the calendar year. So on my next disclosure,
6 this, of course, activity would be disclosed.

7 In addition to that, via
8 conversation -- regular review with the president
9 of the institution, I provide a general report on
10 consulting activities; for example, these
11 activities.

12 HudsonAlpha's policy is faculty members
13 are allowed up to 20 percent of your time towards
14 consulting activities that have a relationship to
15 your research area, such as the evaluation of the
16 biologically plausible mechanism of talc in
17 ovarian cancer. So based on both the timing of
18 the Code of Ethics with regards to the financial
19 disclosure as well as the ad hoc reporting of
20 consulting engagements with the president of the
21 institution, I'm in compliance with the current
22 policies of HudsonAlpha.

23 Q The president of HudsonAlpha is aware
24 of your opinions in this case?

1 A I have not discussed my opinions
2 specifically to this case with him; just the
3 general knowledge that I was asked to participate
4 as an expert witness. He didn't ask, and I
5 didn't provide the content.

6 Q No one at HudsonAlpha is aware of your
7 opinion that talcum powder causes chronic
8 inflammation which can cause ovarian cancer? Is
9 that right?

10 A I have -- I have not specifically
11 shared the contents of the report or -- or my
12 opinions widely at HudsonAlpha.

13 Q Did you disclose last July that you had
14 already been hired and submitted invoices to the
15 plaintiffs' lawyers?

16 A I'm sure I did.

17 Q Do you have that documentation?

18 A No. It's -- it's an electronic
19 disclosure. It's not actually done on paper.

20 Q One of the things that HudsonAlpha does
21 is it partners with the University of Alabama in
22 a comprehensive cancer center; correct?

23 A No, that wouldn't be correct.
24 HudsonAlpha is very specific --

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1 And you may be more familiar with this
2 than I.

3 They're very specific with their use of
4 the word "partnership" and they're, in fact, very
5 specific that they do not engage in a -- anything
6 titled "a partnership." So they -- I would not
7 characterize them as a partner of the University
8 of Alabama Cancer Center.

9 We certainly have -- there are faculty
10 members at University of Alabama Birmingham who
11 are -- have adjunct appointments at HudsonAlpha,
12 just as I have appointments at University of
13 Alabama Birmingham and I am a member of their
14 cancer center.

15 Q Are you aware of the work that
16 HudsonAlpha does with the University of Alabama's
17 Comprehensive Cancer Center?

18 MS. O'DELL:

19 Object to the form. Asked and
20 answered.

21 A I'm aware of some of the work, but I --
22 certainly I -- I don't -- I don't necessarily
23 have knowledge of the full spectrum of those
24 projects, given that they involve many faculty

1 members on both institutions.

2 MS. BROWN:

3 Q Fair to say, then, Doctor, you have not
4 participated in any work with the University of
5 Alabama's Comprehensive Cancer Center?

6 MS. O'DELL:

7 Object to the form.

8 A No, that's not true.

9 MS. BROWN:

10 Q Have you worked with the University of
11 Alabama's Comprehensive Cancer Center on projects
12 involving ovarian cancer?

13 MS. O'DELL:

14 Objection. Asked and answered.

15 A I would -- I would have to review the
16 specific projects that we've -- we've done to
17 answer that.

18 As the codirector of a core facility
19 for the University of Alabama Comprehensive
20 Cancer Center, it is likely that we've worked on
21 some projects related to ovarian cancer, but I
22 can't specifically name them. They are -- I
23 would -- I would characterize them as infrequent.

24 MS. BROWN:

1 Q Have any of those projects attempted to
2 research the potential causes of ovarian cancer?

3 A Again, I'd have -- I'd have to review
4 the projects. They're certainly --
5 fundamentally, most of the questions regarding
6 the analysis of cancer samples are routinely to
7 investigate their cause or their treatment. So I
8 would -- I would answer that question as highly
9 likely.

10 Q Would you agree the cause of ovarian
11 cancer remains unknown today?

12 MS. O'DELL:

13 Object to the form.

14 A No, I would -- I would -- I would not
15 agree that it -- I would not agree to that
16 general statement.

17 MS. BROWN:

18 Q What are the causes of ovarian cancer
19 in your mind, Doctor?

20 A Well, the -- the causes of -- of
21 a -- of any number of cancers, including ovarian
22 cancer, are probably more well understood now
23 than ever, and their complexities I think now are
24 just beginning to be appreciated in the sense

1 that cancer is a disease of unregulated cell
2 growth.

3 Back to our earlier con- -- earlier
4 conversation, some of the fundamental facts that
5 we had discussed and, in fact, I think well
6 replicated in a number of sources, as you pointed
7 out to me, you know, illustrate that there's a
8 milieu of genetic change leading to cellular
9 transformation, and that cellular damage, if we
10 consolidate that as cellular damage, then has to
11 work in concert with a number of other events
12 providing the right environment for a tumor to
13 grow, such as inflammation, chronic or acute.
14 And, so, the -- you know, the -- the -- you know,
15 giving a singular cause would be inappropriate.

16 But I would say the mechanistic causes
17 of cancer are reasonably well understood, but how
18 those apply to the wide diversity of cancer types
19 remains an area of active investigation.

20 I think what's interesting on cancer in
21 general is that there's no -- really no longer a
22 bucket diagnosis. It is -- it -- lung cancer is
23 more complex than lung cancer and ovarian cancer,
24 certainly with the --

1 As I'm sure you're well aware, with the
2 molecular subtypes and other things, it's a
3 complicated disease as well.

4 So to summarize that is -- to summarize
5 all of that complexity by saying that the cause
6 is known or unknown I think would vastly
7 underestimate the -- our current state of the art
8 or knowledge of how complex cancer is as a
9 condition.

10 Q Sure.

11 Scientists, researchers, public health
12 authorities continue to investigate the mechanism
13 by which ovarian cancer is caused. Correct?

14 A That's correct.

15 Q We do not, sitting here today in 2019,
16 have a complete understanding of the etiology of
17 ovarian cancer. Correct?

18 MS. O'DELL:

19 Object to the form.

20 A I would say we have substantial
21 knowledge of factors and exposures that either
22 predispose or directly cause cancer in a large
23 number of -- large number of cancer areas,
24 including ovarian cancer.

1 Now, the -- whether that represents the
2 complete milieu of possibilities is -- is what is
3 currently under research.

4 MS. BROWN:

5 Q Were you aware that the University of
6 Alabama Comprehensive Cancer Center is an NCI
7 center, National Cancer Institute?

8 A Yes. It's -- it's not only an
9 NCI-designated center; it's an NCI-designated
10 comprehensive cancer center, which is a slightly
11 different classification. It's a -- there's more
12 criteria for a cancer center to meet to become
13 comprehensive.

14 Q What does it mean to be an NCI center,
15 to you, if you know?

16 A Stated very simply, it means you have
17 a -- your cancer center is funded by a support
18 grant directly from the National Cancer Institute
19 to provide -- that supports not only patient care
20 but also supports basic research, epidemiology
21 and -- and health outcomes research in cancer.

22 So, in a nutshell, it is a fairly
23 comprehensive grant that supports a wide variety
24 of work within a cancer center that extends

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1 beyond basic -- basic care.

2 Q The National Cancer Institute has
3 funded a number of projects that the scientists
4 at HudsonAlpha are working on. Is that fair?

5 A I'd have to certainly review the grant
6 portfolio. But I'm certain that, since I myself
7 have funding from that cancer center, yes, the
8 NCI does fund some -- some number of
9 investigators at HudsonAlpha.

10 Q And you consider the NCI to be a
11 reputable public health authority; correct?

12 A No, not necessarily. The NCI is really
13 not a public health authority. The N -- the NCI
14 is a -- is a scientific administration center
15 within the National Institutes of Health.

16 Now, I'm speaking of their extramural
17 programs. The NCI also have intramural programs,
18 where they have their own researchers and their
19 own projects. I'm less familiar with those
20 activities.

21 But together, I would state that the
22 NCI is a -- I don't have -- I guess I have not
23 had any experience with the NCI that would lead
24 me to say that they are an authoritative public

1 health authority.

2 Q Before forming your opinions in this
3 case, Dr. Levy, did you look to see what the NCI
4 states about whether talcum powder causes ovarian
5 cancer?

6 A I believe I did see, from a number of
7 statements, certainly potentially from the NCI,
8 regarding the complete opinion and -- and
9 knowledge base for the role of talcum powder in
10 ovarian cancer.

11 Q Do you recall that the NCI has
12 concluded that there's inadequate evidence that
13 talcum powder increases the risk of ovarian
14 cancer?

15 MS. O'DELL:

16 Object to the form.

17 A Which -- what specifically are you
18 referring to? I -- I wouldn't be able to answer
19 that accurately without knowing which specific
20 report or statement that you're referring to.

21 MS. BROWN:

22 Q I'm wondering if, sitting here today,
23 you recall looking at information about the
24 classification of risk factors for ovarian cancer

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1 as done by the NCI.

2 A I don't recall that specifically. I
3 don't also recall seeing any statements from the
4 NCI regarding safety of any product.

5 Q In forming your opinions in this case,
6 Dr. Levy, did you consider the conclusions of
7 public health authorities like the FDA, the NCI,
8 NIH as it relates to talcum powder in ovarian
9 cancer?

10 A So I certainly considered information
11 from each of those entities. But I would make a
12 statement I don't -- I don't recall from any of
13 those entities seeing a single conclusion.

14 Q Is it your opinion, Dr. Levy, that
15 talcum powder causes ovarian cancer?

16 A I wasn't asked to provide an opinion if
17 talcum powder causes cancer. I was -- I was
18 asked to develop an opinion as to the biological
19 plausibility of -- of talcum powder leading
20 to -- leading to change.

21 Now, that's what I was asked from the
22 attorneys. If you're asking -- are you asking me
23 what my opinion is --

24 Q Well, I want to know if, in this case,

1 you are prepared to offer the opinion that talcum
2 powder causes ovarian cancer.

3 A I don't -- I don't think we have the
4 complete information for a sing- -- you know, to
5 have the opinion of a singular cause. But, at
6 the same time, my opinions are that, as stated in
7 the report, there's a clear and well-evidenced
8 biologically plausible role for talcum powder
9 leading to ovarian cancer.

10 Q On page 2 of your report, the second
11 full paragraph that begins "My report
12 consists" --

13 You with me?

14 A Yes.

15 Q -- you state -- you reference your
16 conclusions regarding this cause-and-effect
17 relationship.

18 Do you see that?

19 A I do.

20 Q Do you mean by that that you have an
21 opinion that talcum powder causes the effect of
22 ovarian cancer?

23 A No. That -- that wasn't the meaning of
24 that statement of cause and effect. It was -- it

1 was a -- more of a general statement of a cause
2 being exposure to talc and effect being that
3 biologically plausible mechanism.

4 Q You mentioned a moment ago that you
5 don't think we have the complete info on a
6 singular cause of ovarian cancer. Is that right?

7 MS. O'DELL:

8 Objection to form.

9 A Sorry. Let me read your question
10 again.

11 I have -- I have not seen any evidence
12 that suggests that there is a singular cause of
13 ovarian cancer.

14 MS. BROWN:

15 Q You have not seen sufficient evidence
16 to suggest that talcum powder could be one of the
17 causes of ovarian cancer; correct?

18 MS. O'DELL:

19 Object to the form.

20 A I would disagree. As -- as stated,
21 the -- I have not seen evidence that there's a
22 singular cause of ovarian cancer. I think there
23 is ample evidence that there are a multitude of
24 mechanisms that you can get cellular damage and

1 cellular change within the ovary which then leads
2 to malignant transformation, and that, as stated
3 in the report, there's a biologically plausible
4 mechanism that exposure to talcum powder and its
5 constituents can create those necessary changes.

6 MS. BROWN:

7 Q Do you believe, Doctor, there's
8 sufficient evidence that talcum powder, through
9 chronic inflammation, causes ovarian cancer in
10 some individuals?

11 A No. That -- that was not my -- not my
12 opinion or statement. And I would say
13 specifically chronic inflammation is, again,
14 narrowing the focus in an inappropriate way, and
15 the evidence doesn't illustrate that chronic
16 inflammation is a singular sufficient detail or,
17 I should say, effect to result in ovarian cancer.
18 It's certainly a factor, as -- as well described
19 in the -- in the literature.

20 And -- and, again, I would defer to
21 other expert reports that have similar opinions
22 regarding inflammation, chronic inflammation
23 being one of them.

24 And it may be important to provide an

1 important distinction that cellular damage or
2 what we can refer to as acute inflammation can
3 cause -- certainly has been shown and is
4 well-evidenced that it causes -- can lead to
5 molecular changes that can lead to cancer.

6 Chronic inflammation is a slightly --
7 is in a slightly different biological perspective
8 in that it provides the correct environment for
9 those cancerous changes to take hold and allow
10 malignant transformation, as I mentioned.

11 So I -- I do view them as working in
12 concert but not necessarily independent. So when
13 you ask a question that specifically narrows it
14 to chronic inflammation or even acute
15 inflammation in a singular fashion, you know, my
16 answers will largely be the same, that that's, in
17 and of itself, is too limited to describe as a
18 specific cause, singular or otherwise, of ovarian
19 cancer or of cancer in general.

20 Q You'd agree that the research regarding
21 whether chronic inflammation can cause ovarian
22 cancer is ongoing?

23 A Yes, I would agree it is -- it is
24 ongoing research. But there are a large number

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1 of observations and studies that
2 have -- certainly exist. And, again, their
3 review and -- and content is what went to the
4 opinions in my report.

5 Q And most of the studies that you cite,
6 Dr. Levy, talking about chronic inflammation
7 refer to chronic inflammation as a hypothesis of
8 one of the ways cancer might form in the ovary.
9 Correct?

10 MS. O'DELL:

11 Object to the form.

12 A Let me -- sorry. Let me read your
13 question.

14 No. I would disagree. At least,
15 certainly not most of the studies that I cite.

16 MS. BROWN:

17 Q Do you believe chronic inflammation is
18 an established mechanism of ovarian cancer?

19 A Yes, in the sense that chronic
20 inflammation is a well-established mechanism of
21 cancer in general, including ovarian cancer.
22 This is first observed in the 1800s and has since
23 been -- become well-established in the -- in the
24 cancer field that inflammation plays a

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1 significant role in both the initiation as well
2 as progression of cancer.

3 Q What methodology did you employ for
4 coming to the opinion that chronic inflammation
5 is a well-established cause of ovarian cancer?

6 A Just general mechanism in terms of
7 evaluating biological plausibility.

8 Q I understand, Dr. Levy, you have a
9 general opinion that chronic inflammation can
10 lead to some cancer. Is that right?

11 MS. O'DELL:

12 Objection to form. Misstates his
13 testimony.

14 A I -- I have an opinion regarding the
15 role and importance of inflammation in the
16 initiation and progression of cancer.

17 MS. BROWN:

18 Q And, as it relates to ovarian cancer,
19 what methodology did you employ to arrive at your
20 conclusion that chronic inflammation is an
21 established cause of ovarian cancer?

22 A I -- I did not arrive at that specific
23 conclusion, nor was I asked to.

24 Q You do not believe that chronic

1 inflammation has been established as a cause of
2 ovarian cancer; correct?

3 MS. O'DELL:

4 Object to the form.

5 A No, that -- that's not what I said.

6 MS. BROWN:

7 Q Explain it to me.

8 A I've stated that chronic inflammation
9 or inflammation in general, including chronic and
10 acute infor -- inflammation, is a component and a
11 necessary component for the initiation and
12 progression of -- of cancer as we understand it
13 today. And, in that, cancer, certainly ovarian
14 cancer as well as a variety of other cancer
15 types, is included.

16 Q What methodology did you employ to
17 arrive at the conclusion that ovarian cancer is
18 one of the cancers that can be caused by chronic
19 inflammation?

20 MS. O'DELL:

21 Object to the form. Misstates his
22 testimony.

23 A Yeah. Again, we're not -- I'm not
24 making a specific causal opinion with respect to

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1 any -- whether -- whether inflammation, talcum
2 powder use or other exposures. I -- my -- my
3 opinion in the report is -- is -- was not asked
4 to be a causal opinion.

5 MS. BROWN:

6 Q You reference on page 2 of your report
7 that your opinions are based on assessing and
8 weighing the totality of the evidence, including
9 relevant literature and available documentation
10 and your experience as a geneticist and
11 scientific researcher. Do you see that?

12 A Yes.

13 Q What do you mean by "the totality of
14 the evidence"?

15 A All of the evidence available at the
16 time that I was researching this report.

17 Q All of the evidence concerning what?

18 A Concerning a variety of subjects
19 surrounding ovarian cancer, talcum powder use,
20 and then inflammation and related subjects as my
21 literature review and review of available
22 information progressed.

23 So there was a, I guess, a large number
24 of tangential directions that -- that I examined,

1 from animal models to in vitro studies, in vivo
2 studies, cohort studies, case-control studies.
3 There was quite a broad spectrum of information
4 across a large number of years.

5 Q Do you believe you reviewed the
6 totality of the epidemiology on talcum powder use
7 and ovarian cancer?

8 MS. O'DELL:

9 Object to the form.

10 A I -- I reviewed the available studies
11 that appeared to be relevant for the -- for the
12 opinions that are expressed in my report.

13 MS. BROWN:

14 Q And when you say "available," what do
15 you mean?

16 A Meaning that I could -- I could
17 discover in the scientific literature.

18 Q Did you conduct your own literature
19 searches in connection with your work in this
20 case?

21 A I did.

22 Q How did you go about finding the
23 totality of the evidence relating to whether
24 talcum powder causes ovarian cancer?

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1 A So the -- my methodology for the
2 literature review in establishing my opinion
3 regarding the biological plausibility of talcum
4 powder exposure inflammation and its potential
5 role in ovarian cancer was based on, you know, my
6 activities and many other literature searches, so
7 using a variety of computational tools and -- and
8 web-based resources, from journals to, I would
9 say, primarily PubMed being a resource, but also
10 ISI, Web of Science, Google Scholar and a variety
11 of -- bioRxiv and I'm sure a number of other
12 sources. But those were probably the more
13 primary resources for establishing what
14 literature was available.

15 Q Did you ask the plaintiffs' lawyers for
16 any scientific literature that you used in
17 forming your opinions in this case?

18 A What do you mean by "ask"? There
19 is -- as far as did I ask for their similar
20 process, no.

21 There were some papers that I had
22 identified but was not able to access the full
23 content via the libraries that I have access to.
24 So in some of those cases, specific references

1 that I provided, those full -- that full content
2 was provided by the plaintiffs' lawyer to allow
3 me to review it.

4 Q Did the plaintiffs' lawyers give you a
5 set of epidemiology on which you're relying on to
6 form your opinion?

7 A No, they did not.

8 Q If I look at your report, I see a
9 reference list and then a separate Exhibit B. Is
10 that right?

11 A Yes.

12 Q So, for example, on page 18 of your
13 report, you have a list of literature cited.
14 Correct?

15 A Yes.

16 Let me make sure I have the page
17 correct.

18 Yes, beginning on page 18.

19 Q Is everything that appears in the
20 literature-cited list something that you found on
21 your own, Dr. Levy?

22 A I would have to review the -- the list.
23 But there are certainly --

24 Let me --

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1 I believe the Saed abstracts, as an
2 example --

3 Let me see if there are --

4 No. I -- I believe, in the literature
5 cited, there are certainly some number of
6 examples of information that was provided during
7 the course of the development of my report from
8 the plaintiffs' attorneys in terms of literature
9 for my consideration, but that in no case -- in
10 every case it was provided as a -- as
11 information.

12 The vast majority or nearly the
13 totality of this was information that I had --
14 that I indeed discovered myself and shared with
15 the -- the attorneys, but certainly not complete.

16 Q On page 18 you cite an article by
17 Blount.

18 Do you see that?

19 A Yes.

20 Q Was that given to you by the
21 plaintiffs' lawyers?

22 A I'd have to look at my records. I
23 don't recall.

24 Q Off of the top of your head, are you

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1 relying on information in that article to form
2 your opinions in this case?

3 A No. I'm not relying on any singular
4 article or source to form my opinion on the case.

5 Q Are you relying in part on the
6 information contained in the Blount article?

7 A Since I include it in the cited
8 literature, certainly in some -- in some part.

9 Q What information are you relying on in
10 the Blount article?

11 A I would have to review the article to
12 remind myself where the --

13 Q Take a look at it. We'll pull it right
14 now.

15 What about Paoletti on page 22? Was
16 that something you found on your own or did the
17 lawyers give you that?

18 A So Paoletti --

19 Q Uh-huh.

20 A Page 22?

21 Q Uh-huh.

22 A Actually, the Paoletti one is familiar.
23 That's an interesting one because it's in
24 Italian.

1 Q Are you relying on the information in
2 the Paoletti article to form your opinions in the
3 case?

4 A Again, the -- I wasn't relying on any
5 singular article but instead tried to present and
6 provide reference to as comprehensive a
7 collection of relevant literature in this -- in
8 this space as possible, of which Paoletti,
9 although being in Italian, there were some --
10 enough translated aspects of that that it was
11 worthy to include in the -- in that cited
12 literature as being relevant to the -- to
13 those -- to those opinions.

14 Q Just to make sure we get on the same
15 page here, Dr. Levy, when I ask are you relying
16 on something, I don't mean by that question to
17 suggest it's the only thing you're relying on.
18 And I'll try to say "in part" to make it easy for
19 us. Okay?

20 A Right. Just want to be -- make sure
21 we're clear.

22 Q Absolutely. So do I.

23 And I want to know are you relying in
24 part on anything in the Paoletti article to form

1 your opinions in this case?

2 A I would say in -- in part. As far as
3 my opinions regarding the biologically plausible
4 mechanism that was presented, no, it does not
5 rely on that specific conclusions of that paper
6 but, rather, that paper was included because of
7 its results regarding asbestos contamination in
8 industrial talc, which only support -- add
9 support to the mechanism that I presented in the
10 report.

11 Q Is your opinion in this case, Doctor,
12 based on an assumption that baby powder contains
13 asbestos?

14 A No, it is not.

15 MS. O'DELL:

16 Object to the form.

17 MS. BROWN:

18 Q Is your opinion in this case based on
19 an assumption that baby powder contains
20 fragrances?

21 MS. O'DELL:

22 Objection to form.

23 A My -- my opinion considers the totality
24 of the constituent components of baby powder,

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1 Shower to Shower, you know, under -- either, as
2 we've been referring to it simply as talc or
3 talcum powder or by trade names such as
4 Johnson & Johnson or Shower to Shower, so the --
5 my opinions, as stated in the report, being
6 reasonably -- or trying to be reasonably
7 comprehensive. Therefore, it's not, you know,
8 limited to any -- any singular component, whether
9 it be majority or minority, in the -- in the
10 talcum powder products, as I just stated.

11 MS. BROWN:

12 Q Is your opinion in this case based on
13 an assumption that Johnson & Johnson baby powder
14 products contain heavy metals?

15 MS. O'DELL:

16 Objection to form.

17 A Again, similar to the earlier
18 statement, the opinion is not subject to
19 any -- any singular component. I think the
20 information regarding the -- in deferring to some
21 of the other experts regarding the knowledge of
22 constituent components, whether they be heavy
23 metals or asbestos, only helps to support the
24 biological plausibility of the mechanism I

1 presented.

2 MS. BROWN:

3 Q Do you believe that baby talc alone can
4 cause inflammation that may lead to ovarian
5 cancer?

6 A Based on my review of the literature,
7 there are a number of studies, both of those
8 involving human studies in terms of case
9 controls, as well as a number of animal studies
10 and then, more specifically, in vitro studies
11 that look at talcum powder and its ability to
12 produce clear markers of inflammation.

13 I am -- the -- I am not aware of any
14 specific testing that looked at platy talc
15 individually as a singular component without
16 the -- or out of the context of the products we
17 were just describing in a similar analysis. So I
18 don't -- I don't know that answer.

19 Q Is it your opinion that
20 Johnson & Johnson baby powder products are
21 contaminated with asbestos?

22 MS. O'DELL:

23 Object to the form. Asked and
24 answered.

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1 A I -- I -- I have -- I have been
2 provided expert report, and some of those are
3 referenced in the -- in the report, as we were
4 describing, that describe testing of a number
5 of -- number of samples,
6 included -- Johnson & Johnson included in that,
7 that showed how they -- that the results of those
8 reports showed contamination by asbestos or --
9 or -- or asbestos-like fiber. So, therefore,
10 I've been presented with that evidence.

11 MS. BROWN:

12 Q Have you relied on that evidence in
13 forming your opinions in this case?

14 A Again, no, not -- not as a singular
15 evidence. So, as we just discussed a moment ago,
16 that is a component piece of evidence that
17 leads -- and is supportive of the biologically
18 plausible mechanism described in the report.

19 You know, certainly, it is inarguable
20 that asbestos and asbestos-like fibers cause
21 inflammation. There's also ample evidence of the
22 inflammatory effects of talc. And -- and talc
23 pleurodesis, for example, is -- is designed to
24 produce inflammatory response as a treatment.

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1 So I think, again, similar to the
2 relationship of asbestos and inflammation, it's a
3 well-established scientific fact that talc has an
4 inflammatory role now. Or I should say as of
5 today.

6 Q Have you attempted to quantify, based
7 on the reports of Dr. Longo that you reviewed,
8 how much asbestos contamination is in
9 Johnson & Johnson baby powder products?

10 MS. O'DELL:

11 Objection. Vague as to form.

12 A I --

13 MS. O'DELL:

14 As to the volume and time contained,
15 et cetera.

16 A My -- my answer is simply that I wasn't
17 asked to quantify that as part of my report.

18 MS. BROWN:

19 Q Whether there is asbestos in Johnson &
20 Johnson baby powder products or not does not
21 impact your opinions in this case; is that right?

22 MS. O'DELL:

23 Object to the form.

24 A The opinions regarding the biological

1 plausibility described in my report and its
2 relationship to asbestos are somewhat separate,
3 meaning that I have -- I was not able to discover
4 what the contamination rate or content of
5 asbestos was in any of the referenced studies
6 through the course of my report, so, therefore, I
7 can't comment on the likelihood or -- of -- of
8 how many or any -- or any or all of those samples
9 contain asbestos.

10 MS. BROWN:

11 Q And sounds like you did some work
12 attempting to see if you could calculate a
13 contamination rate. Is that what you were
14 describing?

15 MS. O'DELL:

16 Object -- object to the form.
17 Misstates his testimony.

18 A No. No, not at all. I stated that I
19 didn't have information available to assess
20 either -- either way.

21 MS. BROWN:

22 Q Tell me what you meant when you
23 testified that you were not able to discover what
24 the contamination rate or content of asbestos was

1 in any of the above-referenced studies.

2 MS. O'DELL:

3 Objection. Misstates his testimony.

4 A So reading -- reading back my

5 testimony --

6 MS. BROWN:

7 Q So, Doctor, I see that you're looking
8 at the realtime?

9 A Yes.

10 Q To get clarification on the question?

11 A No. To -- to remem- -- to -- you asked
12 me a question about my statement.

13 Q Correct.

14 A And I was reviewing specifically what I
15 had stated so I could answer your question
16 accurately.

17 Q Terrific. So I want to know what you
18 were talking about when you said you were unable
19 to discover the contamination rate.

20 A To clarify, I was not asked to estimate
21 or determine the contamination rate, and my
22 statement regarding that was in reference to the
23 material I reviewed and the literature that is
24 referenced in my report. I don't recall in any

1 of those studies observing a specific statement
2 of amount of asbestos in the talcum powder
3 products that were under study. So, therefore, I
4 am not able to form an opinion surrounding that
5 contamination rate.

6 Q Would the same be true, Doctor, for
7 heavy metals?

8 A Yes, that's correct.

9 Q And when I say the same would be true,
10 that means you were not able to calculate a rate
11 of heavy metal contamination of any of the talcum
12 powder products in the studies you reviewed?

13 MS. O'DELL:

14 Objection. Vague.

15 A I was not asked to.

16 MS. BROWN:

17 Q Did you attempt to quantify the amount
18 of heavy metals?

19 MS. O'DELL:

20 Objection.

21 A I certainly reviewed the literature to
22 understand what information was available
23 regarding the products that may have been used
24 and what testing may have been done on

1 those -- on those products.

2 MS. BROWN:

3 Q And, as it relates to fragrances, have
4 you calculated the amount of fragrances that are
5 present in Johnson & Johnson's baby powder
6 products?

7 MS. O'DELL:

8 Objection to form.

9 A I -- I wasn't asked to -- to make those
10 calculations. And I would defer to other expert
11 reports that I had an opportunity to review
12 recently that did perform those calculations.

13 MS. BROWN:

14 Q Your opinions in this case are not
15 dependent on whether or not --

16 A I think that was --

17 Q -- there are fragrances in
18 Johnson & Johnson's baby powder; correct?

19 MS. O'DELL:

20 Objection.

21 A Sorry. Let me read that.

22 Sorry. Could you rephrase your
23 question? The question that appears on the
24 monitor is that there are fragrances in

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1 Johnson & Johnson baby powder, question mark.

2 MS. BROWN:

3 Q That's why it's tricky when you read
4 the realtime. Just listen to my question. It'll
5 be more helpful.

6 Your opinion in this case is not
7 dependent on whether or not there are fragrances
8 in Johnson & Johnson baby powder. Correct?

9 MS. O'DELL:

10 Excuse me. Objection to form.

11 You may refer to realtime any time you
12 want to, Doctor.

13 But I object to the form of the
14 question.

15 A So my -- my -- I was -- what was
16 requested of me, again, stating for clarity, was
17 to describe a biologically plausible mechanism
18 for talc and all of its constituent components
19 having a role in inflammation and progression to
20 ovarian cancer based on -- on the information at
21 hand.

22 Certainly the fact, as we've been
23 provided later, the ex- -- the recent review of
24 some other expert reports regarding the

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1 fragrances as well as asbestos, I would say my
2 opinion now is that that information continues to
3 support the biologically plausible mechanism
4 presented in my report.

5 MS. BROWN:

6 Q Your opinion that chronic inflammation
7 is a biologically plausible mechanism by which
8 talcum powder could cause ovarian cancer is not
9 dependent on heavy metals being present in talcum
10 powder; correct?

11 MS. O'DELL:

12 Object to the form. Asked and
13 answered.

14 A My -- my opinions are not based on --
15 on any singular component or constituent because
16 the -- the available information did not
17 scientifically test any singular components
18 or -- or allow --

19 I'm not aware of any studies that
20 examine the inflammatory or other effects of
21 talcum powder that contained heavy metals versus
22 did not.

23 MS. BROWN:

24 Q So, for purposes of your opinions in

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1 this case, for your piece of the puzzle, so to
2 speak, it is not important to you whether or not
3 there are heavy metals in baby powder; correct?

4 MS. O'DELL:

5 Objection to form. Asked and answered.

6 A No, that's not correct. I would say
7 the presence of all of the constituent components
8 is very important for -- from the -- from the
9 perspective of that biologically plausible
10 mechanism, and that includes the type of talc,
11 the structure of the talc, you know, its -- any
12 potential contaminants that are there, as well as
13 the complete spectrum of other constituent
14 components, fragrances, heavy metals.

15 And, of course, fragrances have their
16 own milieu of constituent components that, again,
17 I was not asked to comment on or describe in
18 detail but certainly are part of the overall
19 studies.

20 MS. BROWN:

21 Q You have a conclusion in your report on
22 page 17, Doctor, conclusion number 2, that talcum
23 powder products cause chronic inflammation.

24 Do you see that?

1 A Yes.

2 And I would -- and then my conclu- --

3 Q Hold on. No question yet.

4 A Okay.

5 Q And what I want to know, Doctor, is how
6 do you define the talcum powder products that
7 you've listed here on page 17 of your report?

8 A Primarily the products that are -- when
9 I consider the totality of everything that I've
10 been examining, the talcum powder products,
11 including Johnson & Johnson and Shower to Shower
12 as, you know, I refer to those consumer products
13 under the term "talcum powder."

14 Q What about other consumer talcum powder
15 products? Are they included in your conclusions
16 here on page 17?

17 MS. O'DELL:

18 Object to the form.

19 A So my -- my conclusions are based on
20 the -- on the literature review. And, similar to
21 our discussions regarding contaminants and the
22 ability to quantitate those, many of the studies
23 did not specifically delineate which product or
24 the timing of that product.

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1 In contrast, some of the more recent
2 information available specific to the
3 constituents did meet that definition, so I would
4 say these conclusions apply to both the specific
5 products that I mentioned, Johnson & Johnson and
6 Shower to Shower, as well as potentially other
7 products. But quant- -- quantifying which study,
8 I would have to go through study by study to
9 answer any questions about which specific may be
10 included.

11 MS. BROWN:

12 Q Do you include talc-containing
13 deodorizing sprays in your definition of a talcum
14 powder product?

15 A None of the literature that -- that I
16 reviewed or can recall was limited to those
17 deodorant sprays in terms of a -- as a study
18 variable that I can -- that I can think of.

19 Q I'm not sure what you mean by that.

20 A So the -- the basis of this report was
21 on the talcum powder products, and I don't recall
22 any of the studies that delineated talcum powder
23 as a powder versus a talc-containing deodorant
24 spray as a -- as a variable in the study. So I

1 don't know if any of the studies used -- used
2 that. I'd have to, again, would have to review
3 some of that information to determine if there
4 was a -- if that was a variable in any of the
5 given studies that are the basis of the report.

6 Q What methodology did you employ here in
7 coming to your conclusion that chronic
8 inflammation is caused by talcum powder products?

9 MS. O'DELL:

10 Objection. Asked and answered.

11 A Yeah. Again, to restate, similar to
12 the earlier questions, the -- my methodology was
13 based on standard methodology for establishing
14 biological plausibility, which is a, in a
15 summary, a review of the totality of the evidence
16 and then a summary of that to establish if, based
17 on established or -- or known or factual
18 principles, is there a -- can -- can a mechanism
19 described go from cause to effect in a -- again,
20 in an evidence-supported biologically plausible
21 manner.

22 There's a few references I can provide
23 you that describe that method in a published
24 manner, if that's helpful.

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1 MS. BROWN:

2 Q That would be helpful.

3 A They are -- these are our --

4 MS. O'DELL:

5 These are mine.

6 THE WITNESS:

7 Yeah.

8 There's a -- I can get them --

9 MS. BROWN:

10 Q Are the published methods referenced in
11 your report, Doctor?

12 A No, actually, those are not.

13 Q Okay. How would you go about finding
14 the published methods that contain a description
15 of the methodology you employed in this case?

16 A No. It's that I was just saying that
17 there's a published -- peer-reviewed published
18 article that is the same as the method I used, if
19 you -- if you wanted to review that. I didn't
20 reference this specific paper in the report.

21 Q Okay. And you have a -- do you have a
22 copy of that in front of you right now, Doctor?

23 A I do.

24 Q Okay. So let's mark that as Exhibit

1 14.

2 (DEPOSITION EXHIBIT NUMBER 14
3 WAS MARKED FOR IDENTIFICATION.)

4 MS. BROWN:

5 Q The title of the document is
6 "Evaluating Biological Plausibility in Supporting
7 Evidence For Action Through Systematic Reviews in
8 Public Health."

9 When is the first time you reviewed
10 this document, Doctor?

11 A In the last -- the last day or so.

12 Q Was the document provided to you by the
13 lawyers for plaintiffs?

14 A Yes.

15 Q The document is not referenced in your
16 report. True?

17 A It is not referenced. That's correct.

18 Q You did not review the document prior
19 to writing your report; correct?

20 A That's right.

21 Q The document was something the lawyers
22 for plaintiffs gave you after you had already
23 written and authored your report; correct?

24 A That's correct. I provided that as an

1 example of the -- of a published example of the
2 methodology that I employed.

3 Q You didn't endeavor to research the
4 scientific literature to find a published --
5 published example of your methodology, did you?

6 MS. O'DELL:

7 Objection to form.

8 A I -- it wasn't -- that wasn't what I
9 was -- I wasn't asked to reference the
10 methodology in my report. I was, again, asked to
11 provide an opinion on a biologically plausible
12 mechanism and then, since our discussion has
13 transferred to methodology, to be complete, I
14 wanted to provide an example of a published
15 version of the methodology that -- that is
16 similar to or at least describes in a summary or
17 really in that particular paper an exemplary
18 fashion of the criteria for biological
19 plausibility and the methods used therein.

20 MS. BROWN:

21 Q Exhibit 14 is the product of research
22 the lawyers for plaintiffs conducted on a
23 published article regarding your methodology.
24 True?

1 MS. O'DELL:

2 Object to the form.

3 A No, that's not true.

4 MS. BROWN:

5 Q The lawyers for plaintiffs found
6 Exhibit 14 in the scientific literature; correct?

7 A That's correct.

8 Q In reviewing the scientific literature,
9 did you pay attention to the articles that
10 classify different types of talcum powder
11 products?

12 MS. O'DELL:

13 Object to the form.

14 A Could you give a specific example, and
15 then I --

16 I wouldn't be able to answer without
17 knowing.

18 MS. O'DELL:

19 Q Sure.

20 Do you understand that some of the talc
21 epidemiology separates use by type of talcum
22 powder product?

23 MS. O'DELL:

24 Objection to form.

1 A Again, do you have a specific example
2 of one of the studies so I could -- so I'd be
3 able to accurately answer your question?

4 MS. BROWN:

5 Q Here's what I want to know. Did you
6 look at the studies that separated deodorizing
7 sprays from powder products from cornstarch, for
8 example?

9 A Certainly in my review I made as
10 comprehensive a review of available literature
11 as -- as possible. And, again, if you can name a
12 specific study or one of the references, I can
13 confirm if that was -- if that was part of
14 the -- my review of the epidemiology.

15 Q Do you hold the opinion that talcum
16 powder-containing deodorant sprays causes
17 inflammation?

18 MS. O'DELL:

19 Objection to form. Vague.

20 A So if the --

21 Again, I was asked to provide an
22 opinion on the biologically plausible mechanism
23 regarding talc and talcum powder. So,
24 presumably, any product that contains talcum

1 powder could possibly follow that same
2 biologically plausible mechanism.

3 MS. BROWN:

4 Q Is there a certain amount of talcum
5 powder that a product must contain to cause
6 inflammation?

7 MS. O'DELL:

8 Objection to form.

9 A That wasn't something I was asked
10 to -- to quantify, similar to the discussions we
11 had about metals, fragrances, and asbestos.

12 MS. BROWN:

13 Q In forming your opinion that talcum
14 powder products cause inflammation, you have not
15 attempted to quantify how much talcum powder is
16 in those products; is that right?

17 MS. O'DELL:

18 Objection to form. Asked and answered.

19 A So my -- my review included a number of
20 studies that looked at exposure rates, and my
21 review also included the review of some studies
22 that did not include use frequency as well as use
23 duration. And, so, both of those considerations
24 in terms of my review of the epidemiology were

1 undertaken, but I did not attempt to quantify
2 those relationships specifically.

3 MS. BROWN:

4 Q Okay. So there's two different issues
5 there that I want to ask you about. One, I want
6 to talk to you about whether the talcum powder
7 products you've described on page 17 of your
8 report have a specific composition, in your mind.
9 Okay?

10 Two, I want to talk to you about what
11 you were just answering, which is is there a
12 specific amount of the product that you believe
13 causes inflammation.

14 Do you understand the difference?

15 A I do.

16 MS. O'DELL:

17 Objection to form.

18 MS. BROWN:

19 Q Okay. So let's start, one, with the
20 product. In forming the opinion that talcum
21 powder products cause inflammation, is there a
22 particular chemical composition that you are
23 relying on?

24 MS. O'DELL:

1 Objection to form. Vague.

2 A My -- my opinions are based on the
3 available scientific literature regarding the
4 testing performed on talcum powder and talcum
5 powder products.

6 I -- in my review of those results, I
7 did not see a specific enumeration of any one
8 particular chemical composition that was -- had a
9 greater or lesser cause or effect relationship.

10 MS. BROWN:

11 Q Do you know how much talcum powder is
12 in the Shower to Shower product?

13 A No. I wasn't -- I wasn't asked to
14 quantify that, and I would defer to some of the
15 other expert reports regarding the composition of
16 those products.

17 Q Do you include cornstarch as a talcum
18 powder product?

19 MS. O'DELL:

20 Object to the form.

21 A Cornstarch was included in some of the
22 epidemiology studies, as you -- as you mentioned
23 a moment ago.

24 MS. BROWN:

1 Q Do you consider cornstarch to be a
2 talcum powder product that also causes
3 inflammation?

4 MS. O'DELL:

5 Object to the form.

6 A My -- my review of the literature
7 doesn't -- I'm thinking through the available
8 studies, and I don't recall which studies that
9 may -- may have been a dependent variable in
10 terms of the determination. So I -- I can't
11 answer that. I -- I don't have the information
12 to answer that accurately.

13 MS. BROWN:

14 Q So, sitting here today, you're not sure
15 if cornstarch would be a talcum powder product
16 that causes inflammation as you described on page
17 17?

18 MS. O'DELL:

19 Objection.

20 A No. So --

21 MS. O'DELL:

22 Misstates the testimony.

23 But you may answer if you understand
24 the question.

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1 A So corn -- cornstarch and -- and talcum
2 powder are -- are -- when I'm referring to talcum
3 powder and talcum powder products, cornstarch, as
4 a singular component -- or singular product, is
5 not included in that definition.

6 Now, whether products that contain talc
7 also contain cornstarch, I -- I'm not able to
8 say.

9 MS. BROWN:

10 Q Right. And so that's my question.
11 What about a product like Shower to Shower that
12 contains talc and cornstarch? How have
13 you -- what methodology have you employed to
14 arrive at the conclusion that the Shower to
15 Shower product causes inflammation?

16 MS. O'DELL:

17 Object to the form.

18 A So my -- what I was requested was to
19 write an opinion as to the, again, the
20 biologically plausible mechanism that exposure to
21 talc and its constituents can lead to
22 inflammation.

23 I wasn't asked to provide as to what
24 the minimum or maximum thresholds are of any

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1 product or of any component of that product or
2 constituent.

3 The information I was provided was the
4 analysis of products like Shower to Shower and
5 Johnson & Johnson's product, to evaluate the
6 spectrum of talc and asbestos contamination in
7 some of the constituent components, and then --
8 and, therefore, develop an opinion as to
9 the -- whether or not that those products are
10 supported by the same mechanism that I developed
11 the opinion on, meaning they have the constituent
12 components to cause inflammation.

13 MS. BROWN:

14 Q You have not made a determination of a
15 particular amount of talcum powder that is
16 required to be in a product for it to cause
17 chronic inflammation; correct?

18 MS. O'DELL:

19 Object to the form.

20 A I wasn't asked to provide such an
21 opinion.

22 MS. BROWN:

23 Q Your opinion that talcum powder
24 products cause chronic inflammation is not based

1 on knowledge of how much talcum powder is
2 actually in the product; correct?

3 MS. O'DELL:

4 Objection. Misstates his testimony.

5 A Again, not a -- it wasn't part of -- it
6 wasn't an opinion I was asked to provide.

7 The -- the only -- or, I should say,
8 a -- a study that looked at the -- summarizing
9 the epidemiology literature that I reviewed, some
10 of those studies had a duration and component as
11 far as general talcum powder and talcum powder
12 product use.

13 MS. BROWN:

14 Q And I want to --

15 A I don't --

16 MS. O'DELL:

17 Excuse me. Let him finish.

18 A I was -- I was going to say I don't
19 recall those quantitating the percentage of
20 talcum powder in a -- in a given product in the
21 study.

22 MS. BROWN:

23 Q Right. And, so, you're getting a
24 little into the second question, which I do want

1 to talk about, which is how much people are
2 exposed to.

3 But sticking with just what's in the
4 product, have you made a determination that there
5 is a threshold amount of talcum powder that is
6 required to be in a product before you can
7 conclude that that product will cause chronic
8 inflammation?

9 MS. O'DELL:

10 Objection to form. Asked and answered.

11 A I -- again, I wasn't asked to provide
12 that -- that threshold opinion.

13 MS. BROWN:

14 Q And understanding whether or not there
15 is a threshold of how much talcum powder has to
16 be in a product to cause inflammation is not
17 necessary for you to opine that talcum powder
18 products cause chronic inflammation?

19 MS. O'DELL:

20 Objection. Misstates his testimony.

21 A So my -- my use of the terminology
22 "talcum powder products" includes the product and
23 all of its constituent components, which would
24 be, as we earlier discussed, talcum powder,

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1 fragrances, and any contaminating substances,
2 such as asbestos or -- or heavy metals.

3 And, so, therefore, to -- to more -- to
4 answer -- to be able to answer your question
5 accurately, we would -- I think we would have to
6 have some discussions as to the type of talcum
7 powder and the level of exposure to be able to
8 answer that regarding my opinion in terms of
9 level.

10 You know, the -- to clarify, the --
11 during this research and the -- and having the
12 opportunity to review much of the literature in
13 talcum powder, it's a -- it's a fascinating field
14 because it is similar to asbestos. It appears
15 that the diversity of products and the diversity
16 of talc sources are like having a thorn bush with
17 different size thorns, and, depending on the
18 constituent components, you know, those thorns
19 are bigger or smaller or otherwise. And -- but
20 my opinion is based on the fact that the presence
21 of any of those thorns is sufficient to cause
22 some inflammatory response.

23 MS. BROWN:

24 Q Does a talcum powder product with 10

1 percent talc cause chronic inflammation, in your
2 view?

3 MS. O'DELL:

4 Object to the form. Incomplete
5 hypothetical.

6 A I -- I don't have the information to
7 answer that.

8 MS. BROWN:

9 Q Does a talcum powder product with
10 50 percent talc cause chronic inflammation, in
11 your view?

12 A Again, I don't have the information to
13 answer that.

14 MS. O'DELL:

15 Object to the form.

16 MS. BROWN:

17 Q Is it necessary for you to determine
18 the level of talc in a product before determining
19 that it can cause chronic inflammation?

20 MS. O'DELL:

21 Objection. Asked and answered.

22 A No. My -- my -- so my opinion was
23 asked to answer the question of can -- is there a
24 biologically plausible mechanism from talc

1 exposure to inflammation to the initiation of
2 core progression of cancer. And that's -- that's
3 been the focus of my opinion.

4 MS. BROWN:

5 Q Have you attempted to quantify talc
6 exposure as it relates to individuals?

7 A No, I have not.

8 Again, my -- my opinions are primarily
9 limited to the -- to the biological mechanism.

10 Q Well, isn't that dependent, though, on
11 how much talc a person is exposed to?

12 MS. O'DELL:

13 Objection.

14 A No. Again, separating the -- so the
15 question of the mechanism is --

16 Can an exposure result in a mechanism
17 is separate from how much of an exposure is
18 required to cause that mechanism.

19 MS. BROWN:

20 Q So you've identified two questions for
21 us. One, can exposure result in a mechanism.
22 Correct?

23 A (Nods affirmatively.)

24 Q And, two, how much of an exposure do

1 you need to produce a mechanism. Correct?

2 MS. O'DELL:

3 Objection to form.

4 A Correct.

5 MS. BROWN:

6 Q And, in this case, you have answered
7 question number one, can exposure to talc cause
8 chronic inflammation. Correct?

9 A So my -- yeah. My -- my report details
10 the -- that opinion regarding a biologically
11 plausible mechanism.

12 Q You have not, in this case, answered
13 question number two, which is how much exposure
14 to talc is needed to cause chronic inflammation.
15 Is that right?

16 MS. O'DELL:

17 Objection to form.

18 A I wasn't asked to provide such a
19 mechanism or such a -- such an opinion.

20 Part of my review included some of the
21 epidemiology studies that examine that question,
22 but I certainly would defer to the -- the number
23 of -- of epidemiologists who are -- who are
24 providing testimony in this case, rather than try

1 and paraphrase or opine on their work.

2 MS. BROWN:

3 Q Do you believe --

4 MS. O'DELL:

5 Excuse me. We've been going about an
6 hour and 15 minutes. I'd love to take a break in
7 the next two or three minutes and --

8 MS. BROWN:

9 It will probably take me a little
10 longer than that, but I'm mindful of the time,
11 and I'll just finish this subject and take a
12 break --

13 MS. O'DELL:

14 Well, Dr. Levy, would you like a break
15 now?

16 THE WITNESS:

17 I think we can finish this subject.

18 MS. BROWN:

19 Thank you.

20 THE WITNESS:

21 I -- I'd rather conclude it than break
22 it up.

23 MS. BROWN:

24 Q So, Doctor, as it relates to how much

1 talc is needed to cause inflammation that can
2 cause cancer, that wasn't what you were asked to
3 figure out in this case. Is that right?

4 MS. O'DELL:

5 Objection to form.

6 A No. Well, I -- I was -- I was asked to
7 provide a review of the literature in terms of
8 talc exposure and inflammation and, in that
9 review, identified a number of studies that
10 examined some relationships to dose.

11 But I -- as you -- as you see in my
12 conclusions, none of them speak to dose or
13 duration in terms of that -- of that mechanism.

14 MS. BROWN:

15 Q You are not offering an opinion in this
16 case, Doctor, that perineal use of talcum powder
17 exposes an individual to enough talc to cause
18 chronic inflammation than can cause cancer;
19 correct?

20 MS. O'DELL:

21 Objection to form.

22 A My review of studies that attempted to
23 answer that specific question found a -- or a
24 number of studies, both -- or a number of

1 epidemiology studies found that conclusion and,
2 as -- as reviewed in the report, you know, found
3 an increased risk with increasing -- increasing
4 exposure appears, with the current knowledge in
5 the literature, to increase risk. But my opinion
6 was not to further quantify or further describe
7 that.

8 MS. BROWN:

9 Q Many of the studies you looked at did
10 not show a dose response; correct?

11 MS. O'DELL:

12 Objection to form.

13 A The limitation of several of the
14 studies I reviewed was that they did not examine
15 a dose response, so that, therefore, the study
16 was unable -- unable to make that conclusion
17 because they didn't look.

18 MS. BROWN:

19 Q And some of the studies that did
20 attempt to look at duration and/or frequency did
21 not show a linear dose response. Correct?

22 A I would have to look at the specific
23 studies. But in -- in summary, studies that did
24 look at dose response, particularly more recent

1 studies with larger numbers of participants, the
2 meta-analysis studies, found a significant
3 relationship between duration of use as well as
4 frequency of use in terms of their -- their risk
5 ratios.

6 Q And you are not going to offer the
7 opinion in this case that a woman using Johnson's
8 Baby Powder products perineally is exposed to
9 enough talcum powder to cause chronic
10 inflammation that can cause cancer. True?

11 MS. O'DELL:

12 Object to the form.

13 A I -- I wasn't asked to -- to provide
14 that opinion.

15 MS. BROWN:

16 Q And so, as such, you haven't attempted
17 to quantify how much talcum powder, as used
18 perineally, might get to the ovary. Is that
19 fair?

20 A Again, wasn't -- wasn't asked. I was
21 able to review some of the literature that
22 is -- appears to be long -- longstanding, well
23 established over the last greater than 40 years
24 that show a clear -- and I believe the FDA

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1 statement is -- is describing it as inarguable --
2 that talc can migrate either from perineal
3 exposure or even from inhalation exposure and be
4 found in the ovary.

5 A quantitation of how much exposure is
6 required for that migration to occur and -- or
7 how many times of exposure that migration needs
8 to occur, I think it's been a fairly wide
9 diversity of -- of studies on that subject.

10 And, so, based on that, I'm not able to
11 offer an opinion as to a minimal or maximum dose
12 required to get there, other than -- but,
13 instead, state that there is enough evidence to
14 say factually that migration through the -- or
15 through at least two mechanisms of exposure, talc
16 can be found in the ovary. And I would suggest
17 that -- or I'm not aware of any study that
18 quantitates that further.

19 Q Is it essential to your opinion that
20 talc causes chronic inflammation that can lead to
21 ovarian cancer that some amount of talc be
22 present in the actual ovary?

23 MS. O'DELL:

24 Object to the form.

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1 A So my -- my -- my opinion regarding the
2 biologically plausible mechanism, again, does not
3 rely on duration of exposure or amount of
4 exposure.

5 So, therefore, I would -- I would
6 answer your question directly that it would be
7 no, it does not -- it would not necessarily
8 require talc to be present at the ovary at any
9 given time point for there to be the potential
10 that she had some inflammatory injury due to talc
11 exposure at a previous time.

12 That would, of course, be two different
13 questions, one being effect of exposure and
14 second question being is there clearance of that
15 exposure over time if use is discontinued.

16 So that's, again, two different -- two
17 very different scientific studies would be --
18 would be necessary.

19 MS. BROWN:

20 Q And you have not undertaken either of
21 those studies. Is that fair?

22 A That's fair.

23 Q And -- but essential to your theory,
24 though, Doctor, at some point, some amount of

1 talc has to reach the ovary for the chronic
2 inflammation to occur. Is that right?

3 MS. O'DELL:

4 Objection.

5 A Not -- specific to your question,
6 chronic inflammation, no, not necessarily.

7 MS. BROWN:

8 Q Is it your opinion in this case,
9 Doctor, that a woman can develop ovarian cancer
10 from chronic inflammation from talc without any
11 particle of talc ever reaching the ovary?

12 MS. O'DELL:

13 Objection to form.

14 A No, I didn't -- I -- I certainly did
15 not make that statement. And the --

16 Again, restating the -- this summary of
17 my -- my opinion, that the biologically plausible
18 mechanism for talc exposure to inflammation to
19 cellular damage and then potentially creating the
20 correct environment is based on evidence showing
21 talc exposure in the ovary.

22 MS. BROWN:

23 Q Okay. So critical to your opinion,
24 then, some talc has to get to the ovary at some

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1 time; right?

2 A Well, the -- again, the -- my opinion
3 is not based on how talc migrates or -- or when
4 it can migrate. It's simply based on the, again,
5 that biological premise, that exposure to talc.

6 So I wasn't asked to opine whether or
7 not talc exposure in a neighboring tissue could
8 cause enough of an inflammatory response to
9 affect the ovary.

10 So there is the, certainly, the
11 uninvestigated secondary effects that perhaps
12 talc did not -- is not necessary or -- and
13 required to get to the ovary to cause that
14 effect. I'm -- I'm just not aware of any studies
15 that have made that delineation of talc exposure
16 to neighboring or surrounding organs.

17 There is limited or some suggestion
18 regarding the inflammatory response related to
19 talc exposure in the lung that suggests that any
20 talc exposure causes an inflammatory response.
21 Again, but I can't point you to evidence that
22 would take that inflammatory response and tie it
23 specifically to ovarian cancer.

24 So, again, my answer is there is not

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1 enough evidence to -- to support nor refute that
2 any talc exposure can lead to an increased risk
3 of ovarian cancer. What I do know from my review
4 of the literature is the studies that looked at
5 that specific exposure --

6 And, to be clear, none of the
7 epidemiology studies in humans quantitated the
8 amount of talc reaching the ovary. It was simply
9 the exposure and the -- and the perineal use of
10 talc. So I think any discussion about how much
11 did it reach the ovary and how long was it in the
12 ovary is all hypothetical.

13 Q Why don't we go off the record and take
14 a break.

15 Thank you, Doctor.

16 VIDEOGRAPHER:

17 Going off the record. The time is
18 11:51 a.m.

19 (LUNCH RECESS.)

20 VIDEOGRAPHER:

21 We're back on the record. The time is
22 12:52 p.m.

23 MS. BROWN:

24 Q Welcome back, Doctor.

1 You were asked in this case to assess
2 whether perineal use of talcum powder products
3 induces a biologically plausible mechanism or
4 mechanisms that result in ovarian cancer.

5 Correct?

6 A Correct.

7 Q And define for us, if you will,
8 "biologically plausible mechanism" as you used it
9 in that sentence.

10 A Excuse me. A mechanism that is
11 biologically plausible, I mean that it is
12 supported by either well-established biological
13 facts or supported by at least a single line of
14 evidence in published literature -- you know,
15 generally speaking, peer-reviewed literature but
16 certainly not limited to that -- where when you
17 take -- when you consider the totality of the
18 mechanism, that, essentially, each of the steps
19 makes sense and is -- is supported by -- through
20 either direct or indirect observations.

21 Q Okay. And, in this case, as it relates
22 to talcum powder, do you believe that the
23 biologically plausible mechanism of chronic
24 inflammation causing ovarian cancer is supported

1 by well-established biological facts?

2 A I would say the -- that chronic
3 inflammation as a component of causing ovarian
4 cancer is well established by biologically
5 plausible facts.

6 Q And what are those facts?

7 A I think a number of studies that
8 include the, first, the -- that talc or talcum
9 powder causes inflammation. These exist in a
10 number of forms, including very recent -- recent
11 research by Dr. Saed, as we were -- touched on a
12 little bit earlier in the -- in his paper, as
13 well as classical studies with talc pleurodesis
14 where there's -- you know, the fundamentals of
15 that treatment is the inflammatory response
16 caused by talc.

17 Q Uh-huh.

18 A And, so, that would be the -- some of
19 the -- two examples of where factual information
20 or at least observations that are supportive
21 of -- of that information, you know, being
22 considered as a bio- -- part of a biologically
23 plausible mechanism.

24 Q You would agree, Doctor, that not all

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1 inflammation causes cancer; correct?

2 A I would say inflammation is not
3 singularly responsible for cancer. However, I
4 would clarify that the progression from cellular
5 transformation to malignant cancer, at least with
6 our current understanding of cancer biology,
7 appears to have an inflammatory requirement,
8 meaning that all cases of chronic inflammation
9 don't necessarily cause cancer. However, our
10 understanding of malignant transformation appears
11 to have, universally, an inflammatory component.

12 Q Okay. You would agree, though, that
13 not all types of inflammation that the body
14 experiences is inflammation that will lead to
15 cancer. Correct?

16 MS. O'DELL:

17 Object to the form.

18 A So I would -- taking a step back
19 and -- and -- or to orient us to some of the
20 basis of my opinions and some statements on
21 general cancer biology --

22 MS. BROWN:

23 Q Well, let's start with just the
24 question, though, Doctor.

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1 A Okay.

2 Q Okay. Let's just keep it to an answer
3 to the question. And then if you need an
4 opportunity to make another statement on the
5 record, that's fine.

6 MS. O'DELL:

7 Excuse me. Just object to the
8 direction of the witness.

9 Dr. Levy, you can answer a question
10 however you'd like.

11 MS. BROWN:

12 Q And, just to orient you, Doctor, what
13 I'm after, the question was: Not all
14 inflammation that takes place in the body is
15 inflammation that leads to cancer; correct?

16 MS. O'DELL:

17 Object to the form.

18 A So that, yeah, it's really too general
19 a question. So you're -- you're -- what you're
20 asking is does all inflammation have the
21 potential to have -- have a relationship to
22 cancer, and the answer to that is -- is yes, it
23 does.

24 Now, does every inflammatory response

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1 directly cause cancer? And that's a question
2 that I would say would be reasonable to -- in
3 layperson's terms, in terms of general
4 inflammation, is unlikely.

5 But there -- their distinction
6 between -- is -- you know, stated simply, is
7 inflammation is a -- by our current knowledge of
8 cancer, is a necessary component of cancer
9 progression. That does not equate to all
10 inflammation causing cancer.

11 MS. BROWN:

12 Q Does acute inflammation cause cancer,
13 in your mind, Doctor?

14 A It is a component of the cancer
15 progression process. And, so, in my -- to
16 provide a simplistic distinction between them is
17 a --

18 Acute inflammation which results in
19 either an inflammatory response or direct
20 cellular insult or injury can be viewed as having
21 a -- causing cellular damage that results
22 in -- in cellular transformation.

23 Now, that is not sufficient for that --
24 for those transformed cells to then go on to

1 cause cancer. The -- you need a contribution of
2 other factors. And what those factors are is --
3 some are understood. Some are areas of active
4 research.

5 In the -- in the specific case of
6 ovarian cancer, it does appear, given the
7 late- -- given the observations about latency
8 period, that some level of chronic inflammation
9 appears to be critical, but there is no
10 definition of it being required to then having
11 acute inflammation, again, in summary, causing
12 cellular damage and then chronic inflammation
13 providing a -- a supportive environment for that
14 transformation.

15 And, again, I'm -- I'm generalizing,
16 which, as we discussed earlier in the day, cancer
17 is very complex, and so we have to be cautious
18 with generalizations.

19 Q Talc pleurodesis is a medical procedure
20 by which talc is injected into the pleura;
21 correct?

22 A Correct.

23 Q And it is done that purposefully to
24 elicit an inflammatory response. Correct?

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1 A That's correct.

2 Q And have you looked in consid- --
3 forming your opinions in this case at the body of
4 epidemiology that has followed folks who received
5 talc pleurodesis to see if they developed cancer?

6 MS. O'DELL:

7 Object.

8 A Somewhat, yes.

9 MS. BROWN:

10 Q And are you familiar with the findings
11 of those studies that talc, when injected
12 directly into the pleura for the purpose of
13 causing inflammation, had not caused cancer?

14 MS. O'DELL:

15 Object to the form.

16 A I would disagree with your conclusions.
17 And, in fact, the literature I reviewed has, I
18 think, two fundamental concerns. One is the time
19 period that these patients were followed post
20 pleurodesis, and the other that there -- there
21 have been at least one report, perhaps two -- I
22 would have to review to make sure I'm speaking
23 accurately -- where there was indeed a
24 asbestos-like response in the formation of a

1 mesothelioma-like event in the -- in the -- in
2 the pleural space following talc pleurodesis.

3 However, you know, taking a step back,
4 given the relative rarity of that as a procedure,
5 particularly today, I think drawing conclusions
6 from that as its -- as its relationship to cancer
7 would be difficult, but I -- I do think
8 fundamentally the -- my use of that as an example
9 was not necessarily to tie talc specifically to
10 cancer. It was more to state that it's well
11 established that platy talc individually as it --
12 used in those procedures causes an inflammatory
13 response. And so, you know -- and that is the
14 primary reason I used or reviewed that literature
15 for that purpose.

16 MS. BROWN:

17 Q Is it your opinion, Doctor, that talc
18 pleurodesis leads to cancer?

19 MS. O'DELL:

20 Object to the form.

21 A It is my opinion that talc pleurodesis
22 creates an environment supportive of cancer. And
23 whether or not some number of individuals may
24 progress, could progress or have progressed to

1 cancer is -- you know, is -- is of limited
2 knowledge right now.

3 MS. BROWN:

4 Q What scientific support do you have for
5 your opinion that talc pleurodesis creates an
6 environment supportive of cancer?

7 A Oh, just that it causes an inflammatory
8 response. And, as we've been discussing, there
9 is ample evidence surrounding the role of
10 inflammation in cancer. There's a -- you know,
11 in a number of both reference studies and I think
12 generally, I would -- I would state that it's a
13 generally accepted fact in cancer biology.

14 Q What scientific support do you have for
15 your opinion that talc pleurodesis patients later
16 can and do develop cancer?

17 MS. O'DELL:

18 Object to the form. Misstate his
19 testimony.

20 A I'd have to review my -- review some of
21 the literature. And I can take a look if we want
22 to pause for a moment.

23 But there was -- I recall one study
24 involving talc pleurodesis that was maybe

1 mid-'80s to early '90s. I'd have to, again, have
2 to review that --

3 I gave that specific example of a
4 patient or cohort of patients that were found to
5 have, again, asbestos-like effects in the lung
6 leading to, at least in a case or more than
7 perhaps more than one case, a mesothelioma-like
8 effect like we -- like I just mentioned.

9 But, again, to point you to the exact
10 reference, I'd have to review.

11 MS. BROWN:

12 Q Are you relying on that reference in
13 forming your opinions in this case?

14 A No. Specifically -- again, to restate
15 the -- my description of the pleurodesis process
16 was to support the early part of the biological
17 mechanism that talc causes inflammation. So
18 that -- and, so, in the lung as a tissue, that
19 progression to cancer is -- is -- I think is a --
20 is a -- is a supportive observation to the -- to
21 my overall principle. But, again, it's a
22 separate -- separate exposure type, certainly a
23 very different dosing, potentially, and, again, a
24 very different patient, or the patient is a very

1 different individual in the sense that they
2 obviously have reasons for going through the talc
3 pleurodesis which are -- which are -- which are
4 potentially compounding to the overall phenotype.

5 Q Have you endeavored to quantify the
6 difference between exposure to talc from
7 pleurodesis versus perineal use of cosmetic
8 talcum powder products?

9 MS. O'DELL:

10 Object to the form.

11 A I have -- I have not attempted to
12 delineate those two simply from the perspective
13 that, again, to the biological mechanism, the
14 initial premise is talc causes inflammation. And
15 when I examined literature to look for evidence
16 of that historically, talc pleurodesis is one
17 example of inflammation. There's now others, and
18 there's, subsequent to that, there's been
19 a -- now a number of -- or, you know, probably
20 a --

21 Dr. Saed is one example of a reasonably
22 comprehensive molecular study examining specific
23 inflammatory markers tied specifically to
24 cellular exposure to, in the case of that paper,

1 specific products, you know, such as the Shower
2 to Shower and the -- and baby powder.

3 MS. BROWN:

4 Q Do you believe the inflammation caused
5 by talc pleurodesis is chronic inflammation that
6 leads to cancer?

7 MS. O'DELL:

8 Objection to form. Asked and answered.

9 A Again, I believe the inflammatory
10 response to talc exposure, which would include
11 talc pleurodesis, induces an inflammatory
12 response that would be supportive of cancer
13 development and/or progression.

14 MS. BROWN:

15 Q And what scientific literature other
16 than the one study you just referenced for us do
17 you rely on for your opinion that talc
18 pleurodesis induces an inflammatory response that
19 would be supportive of cancer development and/or
20 progression?

21 MS. O'DELL:

22 Object to the form.

23 A All my -- my opinion is based on
24 connecting two basic concepts. Talc exposure

1 causes inflammation. Inflammation has a
2 significant role in cancer development.

3 And, so, as far as -- each of those is
4 supported by individual -- individual studies,
5 and -- and now -- as I mentioned, there are now
6 studies that directly tie those together in
7 observation.

8 MS. BROWN:

9 Q What is the scientific basis for your
10 support that talc exposure causes the type of
11 inflammation that has been linked to cancer?

12 A The most recent is the Saed publication
13 that we discussed and -- or at least has been
14 mentioned. In that study, looking at -- there
15 was a assessment and, in some cases, a
16 quantitation of the specific molecular markers
17 for inflammation that were induced, and many
18 of -- some of those markers are shared with known
19 markers for -- for cancer progression, such as
20 CA 125, as well as others.

21 Q Are you referring to Saed's 2018 paper,
22 Dr. Levy?

23 A Yes.

24 Q And you formed the opinions that talcum

1 powder products cause chronic inflammation in
2 your November 2018 report before having seen the
3 Saed paper from 2018; correct?

4 MS. O'DELL:

5 Object -- object to the form.

6 Misstates his testimony.

7 A The -- so, as we discussed -- we
8 discussed earlier, I had seen abstract
9 information as well as earlier publication from
10 Dr. Saed's group and that the current 2018 paper,
11 while not necessary for the opinions described in
12 the report, certainly support those opinions,
13 given that it was a direct assessment of specific
14 products, specific -- in specific doses applied
15 to cellular material and then measurements for
16 inflammation made directly on that material.

17 So while that particular study was
18 not --

19 And, again, the -- the earlier studies
20 that were used to inform the 2018 paper were
21 certainly used in this report and referenced
22 the --

23 And I'm just recalling when. Or if
24 we've refer- -- had the opportunity to reference

1 the --

2 Yeah. So we reference primarily the
3 abstracts and then, again, as well as some of the
4 other Saed work, which is the foundation of the
5 directed studies that are described in the
6 Reproductive Sciences paper that is Exhibit 12.

7 MS. BROWN:

8 Q Do you know that Dr. Saed is a paid
9 expert for the plaintiffs' lawyers in this
10 litigation?

11 A I am aware. Yes.

12 Q Have you considered that fact in
13 evaluating Dr. Saed's work?

14 A I did.

15 Q Other than Dr. Saed's work from 2017
16 and 2018, what evidence are you relying on to
17 support your opinion that talcum powder produces
18 the type of inflammation that can lead to cancer?

19 A There has been -- looking through
20 the -- there's the Buz'Zard and Lau, 2007. We
21 were discussing the Hamilton -- Hamilton paper in
22 terms of immune response but then, more
23 specifically, the NTP reference in 1993. And in
24 those cases, that was either looking at increases

1 in reactive oxygen species generation --

2 THE COURT REPORTER:

3 Wait a minute. You have to slow down
4 when you read, please.

5 MS. O'DELL:

6 You may continue.

7 A Just to -- before I left off, I think,
8 in those mentioned references, the reactive
9 oxygen species generation, increased cell
10 proliferation, and the use of -- in the specific
11 case of Buz'Zard and Lau, was looking at the
12 transformation in human ovarian cancer cells that
13 were treated with talcum powder -- sorry -- human
14 ovarian cells treated with talcum powder.

15 MS. BROWN:

16 Q Other than Buz'Zard, Hamilton, and NTP,
17 is there anything else that you are relying on to
18 support your opinion that the inflammation caused
19 by talcum powder is the type of inflammation that
20 causes cancer?

21 A So there's additional references
22 mentioned in the report; Gates, Belot, Harper and
23 Saed. And then, in addition to that, there was
24 a --

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1 Make sure I'm referring to the right
2 one.

3 So those were the -- those were the
4 primary references. And then, of course, there
5 were supporting materials and other earlier-cited
6 work.

7 But for the opinion regarding the type
8 of inflammation that is caused by exposure to
9 talc and as far as its specific relationship to
10 cancer, there's -- there's -- I would point to
11 the, at least in the Saed work, the specific
12 quantitation of a very well-known tumor marker,
13 CA 125, also known as mucin-16 elevation in that
14 work, and then, in the case of Gates, some of the
15 fundamental glutathione S-transferase has been
16 associated or has been observed as a higher risk.

17 And, so, that would -- those would be
18 some examples.

19 Q Are you aware of any animal study,
20 Dr. Levy, that shows the inflammation caused by
21 talcum powder causing precancerous changes?

22 MS. O'DELL:

23 Object to the form.

24 A I would have to review the -- a few of

1 the details, and I -- there -- I am aware
2 of -- mentioned earlier the Woodruff or Woodford,
3 the earlier 1971 paper where I couldn't remember
4 the author, is one of the earliest studies that I
5 came across that had -- it has an animal model
6 study.

7 MS. BROWN:

8 Q Doctor, is it your testimony that --

9 First of all, do you think it's -- that
10 in opining that there is a biologically plausible
11 mechanism by which talcum powder causes chronic
12 inflammation that can cause ovarian cancer, is it
13 necessary, in your mind, to be able to show in
14 animals that talcum powder does just that?

15 A That talcum powder causes inflammation?

16 Q That causes ovarian cancer.

17 A No, I don't -- I don't think that

18 that's -- that's certainly not a requirement.

19 And the reason I -- the reason I give that answer
20 is -- is quite simple; that there is a wide
21 diversity of animal model studies that have not
22 been able to mimic specifically or correctly
23 human cancer for both -- both from a detection
24 and most often from a treatment perspective,

1 meaning that, fundamentally, humans and most --
2 or at least the animal systems used as -- in
3 scientific modeling are different. Some of their
4 differences are due to different pathways, and
5 others of the differences are due to actually,
6 you know, fundamental immune system differences.

7 Q The Hamilton article that you
8 identified for me, we marked earlier in the
9 deposition as Exhibit 7. Do you recall that?

10 MS. O'DELL:

11 Counsel, would you mind just placing
12 the exhibits by the witness so he can refer to
13 them as he'd like, please.

14 A Yes, I recall this.

15 MS. BROWN:

16 Q And you would agree with me, Doctor,
17 that the Hamilton study that we discussed this
18 morning concluded that there were no neoplastic
19 changes in the animals that were injected with
20 talcum powder; correct?

21 MS. O'DELL:

22 Object to the form. Asked and
23 answered.

24 A No. No, I -- I wouldn't agree.

1 MS. BROWN:

2 Q What evidence in Hamilton, Doctor, are
3 you relying on to support your position that
4 Hamilton showed neoplastic changes in animals
5 injected with talc?

6 A Well, I'm not -- I'm not stating that
7 Hamilton specifically showed that.

8 What I'm stating is that -- that there
9 is a Hamilton study as an animal model system to
10 make the conclusion that, in this animal model
11 system, that talc or talcum powder does not -- or
12 that causes or does not cause ovarian cancer is
13 not -- it's -- it is -- it has limitations.

14 And, as we discussed a bit earlier, the
15 two limitations are the very limited time points
16 of the animals. And if we look at the relative
17 and observed time points that we know now, as far
18 as latency period, these are well short of
19 those -- of those periods, even by rat standards,
20 and then the number of treated animals is
21 relatively small at ten. So the...

22 Q Doctor, do you rely on the Hamilton
23 article to support your opinion that talcum
24 powder produces chronic inflammation that causes

1 ovarian cancer?

2 A No, I don't rely -- again, I don't rely
3 on any -- there's not a reliance on any singular
4 article.

5 Q Did not mean to suggest that, Doctor.

6 I asked you for the scientific support
7 that you have for the opinions you're giving in
8 this litigation, and one of the articles you
9 identified was the Hamilton article. Correct?

10 A Uh-huh. Yes.

11 Q And I -- and this Hamilton article, as
12 we discussed, at page 103, found no evidence of
13 neoplasm in the rats injected with talc. Right?

14 A They -- I -- I don't -- they did
15 not -- I don't recall seeing a description of
16 neoplasm in the Hamilton article.

17 Q Page 103, second column, begins with
18 "No evidence."

19 A "No evidence of cellular atypia."

20 Q Uh-huh. "And concludes that in no
21 ovary was there any evidence of frank neoplasia";
22 right?

23 A Yes. That's what's written in the
24 paper.

1 Q So this article looked at talc that was
2 injected into animals and found no evidence of
3 changes that lead to cancer. Correct?

4 MS. O'DELL:

5 Objection to form.

6 A Over the time period that they -- that
7 the study was performed, they did -- they did
8 not -- they did not report, and, in fact, as you
9 said, their statements are "no evidence of
10 cellular atypia or mitotic activity."

11 MS. BROWN:

12 Q So in opining, as you do in this case,
13 that talcum powder can biologically induce
14 chronic inflammation that causes ovarian cancer,
15 what methodology did you employ to consider the
16 findings of the Hamilton article?

17 A Well, I considered the findings of the
18 Hamilton article, as -- as referenced in the
19 report, primarily showing that talc has an
20 inflammatory or an immune response. And that was
21 the primary inclusion of the -- of the Hamilton
22 paper.

23 Q Not all inflammatory or immune
24 responses lead to cancer; right?

1 MS. O'DELL:

2 Objection. Asked and answered.

3 A As -- as we discussed, not -- not all
4 inflammatory responses have been shown to
5 conclusively lead to cancer. And, so...

6 MS. BROWN:

7 Q And Hamilton does not support the
8 opinion that the type of inflammatory response
9 that talc causes is the type that causes cancer.
10 Fair enough?

11 MS. O'DELL:

12 Object to the form.

13 A No. I would say that's unfair.
14 Because, again, the limitation of the Hamilton
15 study at the time it was performed was -- is a
16 very short timeline. So there is -- it is an
17 incomplete study in the sense that there is
18 certainly the possibility that the first aspect
19 or the first event that we're -- that we've been
20 discussing in cancer biology, the cellular damage
21 to lead to transformation, could have occurred in
22 some of the rat tissues but had not progressed
23 enough or had -- or had taken hold enough to
24 cause or to have that be detected in this

1 particular study performed in the early '80s.

2 And, furthermore, rat -- the rat model
3 for human cancer, since this study has been in
4 other cases, has some limitations as it relates
5 to how applicable it is to the human condition.

6 MS. BROWN:

7 Q The NTP study that you identified as
8 supporting your opinion, Doctor, that also does
9 not show evidence of neoplastic changes; is that
10 right?

11 MS. O'DELL:

12 Object to the form.

13 Doctor, please feel free to refer to
14 the study if you need to.

15 A Yeah. I'll do that now.

16 (DEPOSITION EXHIBIT NUMBER 15
17 WAS MARKED FOR IDENTIFICATION.)

18 MS. BROWN:

19 Q Doctor, we'll mark as Exhibit 15 to
20 your deposition the NTP study to which you were
21 referring.

22 A Uh-huh.

23 Q And this study, as well, does not show
24 evidence of neoplastic changes.

1 MS. O'DELL:

2 Object to the form.

3 Do you have a copy for me?

4 It's what number?

5 MS. BROWN:

6 Fifteen.

7 A I think the -- the important
8 distinction in this particular study is this was
9 an aerosol-based -- based study. It certainly
10 was longer than the Hamilton but was -- was not a
11 study that mimics the perineal use of talc.

12 MS. BROWN:

13 Q And, so, as it relates to your opinion
14 in this case, Doctor, that talc induces a chronic
15 inflammation that can lead to ovarian cancer, the
16 NTP study does not support that, does it?

17 MS. O'DELL:

18 Object to the form.

19 A I would say the study does support my
20 opinion regarding talc and its role in
21 inflammation. And if we refer to page 6 within
22 the first -- the first paragraph, beginning with
23 "Accumulations of macrophages."

24 MS. BROWN:

1 Q Did you review, Doctor, the --

2 And -- and what about the findings of
3 NTP support your opinion?

4 A Well, first, the inflammatory response,
5 given the evidence by the accumulation of
6 macrophages, and then, secondly, that in the
7 female rats, the incidences of alveolar and
8 bronchial or adenoma, carcinoma, and adenoma in
9 the 18-milligram-per-meter group were
10 significantly greater than those of controls.

11 Q So did you consider the FDA's findings
12 as it relates to the evaluation of the NTP study?

13 MS. O'DELL:

14 Object to the form. Vague.

15 A Which -- which FDA?

16 MS. BROWN:

17 Q Have you considered, in connection with
18 this case, the FDA's response to the 2014
19 citizens petition?

20 A Yes. That's familiar. And if I recall
21 correctly --

22 Or do you have -- is that handy?

23 Q We'll mark that as Exhibit 16, Doctor.

24 (DEPOSITION EXHIBIT NUMBER 16

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1 WAS MARKED FOR IDENTIFICATION.)

2 MS. BROWN:

3 Q The reason I want to talk to you about
4 this is it contains a review of the NTP study we
5 were just discussing.

6 First of all, did you consider this
7 document in connection with your opinions in this
8 case?

9 A Yes, this document's familiar.

10 Q Okay. And do you recall that a cancer
11 prevention coalition wrote the FDA requesting
12 that a warning label be placed on talcum powder
13 products?

14 A Yes.

15 Q And do you recall, as evidenced on
16 page 1, the FDA reviewed the data as it related
17 to that question?

18 A I -- I recall that the FDA reviewed the
19 data and determined that it was insufficient, and
20 they did not identify any new compelling
21 literature at the time. But this was in 2014.

22 Q And the NTP --

23 MS. O'DELL:

24 Excuse me, counsel.

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1 Were you finished? If you're finished,
2 that's fine. I just didn't know if you completed
3 your --

4 A I'm just reading. There was one
5 other -- I recall --

6 MS. BROWN:

7 Q Doctor, the NTP study that you pointed
8 us to was from 1993. Is that right?

9 A I believe that's correct.

10 Q All right. And one of the things that
11 the FDA did in this letter of 2014 is reviewed
12 that study; correct?

13 A Yes.

14 Q And I'll direct you to page 3 of 7.
15 And what the FDA concluded was that the study
16 lacked convincing scientific support because of
17 serious flaws in its design and conduct.

18 Do you see that?

19 MS. O'DELL:

20 Where are you reading? Sorry.

21 MS. BROWN:

22 Page 3. Page 3.

23 MS. O'DELL:

24 Oh. Page 3. Sorry. I thought you

1 said page 2. I'm sorry.

2 MS. BROWN:

3 Q Do you see that, Doctor?

4 A Starting with --

5 Q Bottom of page 3 --

6 A -- under toxicology findings?

7 Q So, to orient us here, Doctor, you
8 pointed, as evidence of support of your opinions
9 in this case, to the NTP study. Right?

10 A Correct.

11 Q And the folks who wrote to the FDA
12 requesting a warning on talc, they, too, pointed
13 to that study; right?

14 A Yes.

15 Q All right. And, so, the FDA reviewed
16 that study and, in the letter denying the
17 citizens petition, included its critique of that
18 study; correct?

19 A Correct.

20 Q And one of the things the FDA concluded
21 was that the study had serious flaws. True?

22 MS. O'DELL:

23 Objection to form.

24 A I don't -- do you -- I don't see where

1 the FDA claimed serious flaws.

2 MS. BROWN:

3 Q At the bottom of page 3 --

4 A I see.

5 Q -- the sentence that begins, "However,
6 this study lacks convincing scientific support
7 because of serious flaws in its design and
8 conduct -- and conduct."

9 Do you see that?

10 A I do.

11 Q And one of the things the FDA points to
12 is that the investigators used micronized talc
13 instead of consumer grade talc, resulting in the
14 experimental protocol not being reflective of
15 human exposure conditions in terms of particle
16 size.

17 Do you see that?

18 A I do.

19 Q Have you made a determination in this
20 case, sir, about the size of the particles in
21 talcum powder products?

22 A I -- I've not made that distinction.

23 And --

24 Q There's --

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1 A And, furthermore, I think the --
2 importantly, the -- the flaws that the FDA points
3 out are, you know, not in disagreement with
4 our -- with our discussions surrounding both the
5 inflammatory response and then some of the
6 results there. I don't -- I don't see as a
7 concern --

8 In fact, the -- it appears the FDA does
9 not disagree with the observation of the evidence
10 of carcinogenic activity in the non-asbestiform
11 talc. I think they --

12 I share --

13 Q Let's focus back on the question,
14 Doctor.

15 MS. O'DELL:

16 Excuse me. Let him finish his answer.
17 He's not finished.

18 A So, the, you know, the serious flaws
19 were the, I think, in this case, the specific
20 inclusion of nonasbestos talc and use of
21 micronized talc instead of consumer grade. So I
22 think in that -- in that sense, it's not
23 surprising that it had a different -- perhaps a
24 different response than may be observed with

1 consumer products or talc that have -- may have
2 contaminants, whether it be asbestos or other.

3 MS. BROWN:

4 Q Do you remember the question I asked,
5 Doctor?

6 A Perhaps it would be helpful to restate.

7 Q I think, probably.

8 I asked if you had made a determination
9 in this case about the size of the particles in
10 talcum powder products.

11 A I -- so as far -- a determination, no.
12 I would -- I would say I have had an opportunity
13 to, you know, review or become more educated in
14 the diversity of talc products and the
15 interesting geographic relationship to different
16 size particles and -- in the presence or absence
17 of asbestiform particles in talc, which was a,
18 you know, fascinating area to become educated in.

19 As far as examining that in each of the
20 individual studies, I certainly was able to pay
21 attention to earlier or later studies as it
22 applied to when there was a specific description
23 of the talc, such as in the NTP study where
24 there -- that was one of the few that had a

1 specific determination.

2 But I was basing my opinions on the
3 general behavior, summarized behavior of talc
4 based on the available evidence.

5 Q In forming your opinions in this case,
6 Doctor, have you concluded that a particular
7 route of exposure is more likely when women are
8 using talcum powder products perineally?

9 MS. O'DELL:

10 Object to the form.

11 A Certainly it would seem logical that
12 the route of talc exposure would be related to
13 the area that the talc is used.

14 MS. BROWN:

15 Q As such, do you believe and have you
16 assumed for purposes in your -- of your opinions
17 in this case that talc more likely migrates from
18 the perineum to the ovaries, as opposed to talc
19 being inhaled and then traveling down to the
20 ovaries?

21 A The evidence I've seen would suggest
22 that that migration that you described from the
23 perineum through the vagina into the fallopian
24 tubes into the ovary is certainly far more likely

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1 when -- when used in the perineum compared to
2 inhalation.

3 But I have not seen a study that tried
4 to distinguish that in terms of having an exposed
5 group who inhaled talc only and then looked for
6 evidence of the presence in the ovary.

7 Q Back to the FDA document we were
8 discussing, Doctor, the FDA's critique of the NTP
9 study continues on page 4, where the FDA
10 identifies that the investigators conceded they
11 have problems with the aerosol generation system
12 and that the study did not include positive and
13 negative dust controls.

14 Did you consider those critiques in
15 evaluating the NTP study in this case?

16 MS. O'DELL:

17 Object to the form.

18 A Well, I -- I certainly considered --
19 you know, considered them in -- as -- as I would
20 consider any -- any other evidence or opinion
21 on -- on these relevant subjects.

22 MS. BROWN:

23 Q The FDA went on to conclude, Doctor,
24 that, in light of the shortcoming, a panel of

1 experts at the 1994 ISRTP/FDA workshop declared
2 that the 1993 NTP study has no relevance to human
3 risk.

4 Do you share that conclusion?

5 MS. O'DELL:

6 Object to the form.

7 A I do not. And I think, importantly,
8 you know, even there at the bottom of page 4,
9 their point number 4 saying a cogent biological
10 mechanism by which talc might lead to ovarian
11 cancer is lacking.

12 MS. BROWN:

13 Q Uh-huh.

14 A I believe, as we're discussing today,
15 subsequent research and subsequent studies
16 have -- and including my report, have helped
17 define that plausible biological mechanism
18 which -- by which talc may lead to ovarian
19 cancer.

20 Q In answering my question, Doctor, you
21 pointed to a different portion of the same page
22 we were discussing; correct?

23 A Correct.

24 Q And what you pointed to was the FDA's

1 conclusion here in 2014 that a cogent biological
2 mechanism by which talc might lead to ovarian
3 cancer is lacking. Correct?

4 MS. O'DELL:

5 Object to the form.

6 A I -- I would disagree in the general
7 nature of your statement and clarify it by saying
8 the FDA found a lack of that mechanism based on
9 the submitted literature of the citizen petition.

10 MS. BROWN:

11 Q So do you understand, Doctor, in
12 evaluating the FDA's response, that they, in
13 fact, did their own investigation in addition to
14 the literature that was provided to them at the
15 time?

16 MS. O'DELL:

17 Objection. Misstates the record.

18 A Well, my reading of it, it says
19 they -- that their -- that the scientific
20 literature considered was submitted in support of
21 both citizen petitions. And...

22 MS. BROWN:

23 Q Are you finished, Doctor?

24 A Yes. I was just looking to see if

1 there was a notation about further --

2 Q I'll direct you, Doctor, to page 4, the
3 second full paragraph that begins "In addition,
4 the FDA stated."

5 "In addition, we reviewed relevant
6 toxicity literature (consisting of 15 articles
7 from 1980 to 2008) not cited in your petition to
8 determine if there was additional support at this
9 point in time for your suggested warning label."

10 Do you see that?

11 A I do.

12 Q And, based on the FDA's review of all
13 the literature that they investigated at the
14 time, they concluded that a cogent biological
15 mechanism by which talc might lead to ovarian
16 cancer was lacking. Right?

17 MS. O'DELL:

18 Objection to form.

19 MS. BROWN:

20 Q That was their conclusion; correct?

21 A Yes, as written, that was their -- that
22 was the FDA's conclusion.

23 Q And you, Dr. Levy, disagree with that
24 conclusion; correct?

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1 A I -- I disagree with the -- or I -- I
2 have found, based on a review of the literature,
3 that there are now additional supporting studies
4 that would -- that would refute some of these
5 conclusions of -- by the FDA review.

6 Q And explain to us, then, Doctor, what
7 methodology you employed or what research you
8 conducted to reach a conclusion different from
9 the FDA's conclusion in 2014.

10 A I think, similar to what the FDA
11 described, my review is of the literature now,
12 you know, through 2018, examining the available
13 information regarding inflammatory response to
14 talc and then talc exposure as it relates
15 to -- to the initiation of progression of cancer.

16 Q Dr. Leavy -- Dr. Levy, do you think
17 that the FDA, in concluding, as they did in 2014,
18 that a cogent biological mechanism by which talc
19 might lead to ovarian cancer is lacking, do you
20 think they were wrong at that time?

21 A I would -- I -- I would say that they
22 were incomplete at that time. And, in fact, you
23 know, one of the --

24 If we -- if we look at page 5 in the

1 one, two -- third full paragraph beginning with
2 "while there exists," where the FDA does agree
3 about the -- that it's plausible that perineal
4 talc and other particulates reach the endometrial
5 cavity and -- and associated organs and may
6 elicit a foreign-body-type reaction and
7 inflammatory response that in some exposed women
8 may progress to epithelial cancers. What they do
9 state, "However, there has been no conclusive
10 evidence to support causality."

11 So I would suggest that this paragraph
12 is in support of the biologically plausible
13 mechanism that I included in the report and
14 that -- and, as we've been discussing, I
15 haven't -- we -- we've not been discussing a
16 causal or a formal causal evaluation.

17 Q What information did you rely on,
18 Doctor, in reaching the conclusion that there is
19 a biological mechanism that the FDA did not?

20 MS. O'DELL:

21 Object to the form. Misstates his
22 testimony.

23 A I'm stating that the -- as we
24 discussed, as we've been discussing today, the --

1 the response to talc -- the response to talc
2 exposure as an inflammatory response is supported
3 by a number of studies, including the NTP study,
4 which, although the FDA had some concerns with,
5 the FDA also made statements regarding the
6 exposure to talc and other particulates having an
7 inflammatory response and that some exposed
8 women's may have progressed to epithelial
9 cancers.

10 So, again, they're -- I think
11 they -- they're in agreement there. So even the
12 concerns with the study withstanding, there's --
13 there's -- there's -- I still -- I still think
14 the FDA report is in support of the mechanism
15 that we've been discussing.

16 MS. BROWN:

17 Q The FDA concludes that a cogent
18 biological mechanism by which talc might lead to
19 ovarian cancer is lacking, do they not?

20 MS. O'DELL:

21 Objection to form. Asked and answered.

22 A But I would al- -- I would say the FDA
23 contr- -- perhaps contradicts itself later in the
24 same document, stating that there is both an

1 inflammatory response and that in some exposed
2 women they may progress to epithelial cancer.

3 MS. BROWN:

4 Q Other than the Woodruff article,
5 Doctor, are you aware of any other study in
6 animals that shows inflammation leading to
7 cancer?

8 MS. O'DELL:

9 Objection to form. Other than those
10 he's mentioned?

11 A Yeah. I -- I would have to -- that
12 would -- that would require review of the
13 literature to -- to speak generally to animal
14 studies and inflammation leading to cancer.

15 MS. BROWN:

16 Q Let me rephrase.

17 In terms of your opinion here that talc
18 causes chronic inflammation that causes ovarian
19 cancer, you identified the Hamilton study, the
20 NTP study, and the Woodruff study as animal
21 studies that support that view. True?

22 A I identified those studies as
23 supportive of my -- of my opinion, yes.

24 Q Are you aware of any additional animal

1 studies on which you're relying?

2 A Not -- not for the contents of the
3 report. Not that I'm aware of. I think we've --
4 we've already discussed some of the other
5 references contained in the report
6 below and -- or at least by mention and Gates.

7 (DEPOSITION EXHIBIT NUMBER 17
8 WAS MARKED FOR IDENTIFICATION.)

9 MS. BROWN:

10 Q I'm gonna mark as Exhibit 17 to your
11 deposition the Buz'Zard study that you mentioned
12 a moment ago. Do you recall that?

13 A Yes.

14 Q Do you rely on the Buz'Zard study in
15 supporting your view that chronic inflammation
16 from talcum powder use can cause ovarian cancer?

17 MS. O'DELL:

18 17?

19 MS. BROWN:

20 Yes.

21 A Sorry. Can you restate your question?
22 It wasn't...

23 MS. BROWN:

24 Q Do you rely on what we've marked as

1 Exhibit 17, the Buz'Zard study, to support your
2 view that talcum powder causes chronic
3 inflammation that leads to ovarian cancer?

4 MS. O'DELL:

5 Object to the form.

6 A As we've discussed, not singularly, but
7 the -- as part -- as part of a complete picture
8 of talc causing reactive oxygen species
9 generation and other inflammatory responses,
10 certainly this is a study that supports that
11 opinion.

12 MS. BROWN:

13 Q Did you consider the type of cells that
14 were evaluated in the Buz'Zard study?

15 MS. O'DELL:

16 Objection to form. Vague.

17 A Certainly in terms of the overall
18 experimental design.

19 MS. BROWN:

20 Q Did those -- were those normal human
21 ovarian cells?

22 A The -- the author has labeled them as
23 normal human ovarian cells. But the -- you know,
24 one of the key characteristics and similar to our

1 comments on -- on animal systems is all -- all
2 in vitro or in vivo studies that are using cell
3 lines or animals have limitations. And in this
4 case, you know, cell lines are particularly
5 notorious in research in general for
6 their -- for -- having to use care in extending
7 findings to, you know, broad mechanisms in a --
8 in a complex organism or in the human body.

9 Q Sure.

10 What you're -- what you're saying is
11 you've got to be careful taking the findings from
12 one cell study and extrapolating that to humans.
13 Fair?

14 MS. O'DELL:

15 Object to the form.

16 A The -- I think you have to be careful
17 in evaluating each study in using the relevant
18 components of that study and observations in that
19 study as part of an overall mechanism and whether
20 it's supportive or refutes such a mechanism.

21 So --

22 MS. BROWN:

23 Q Did -- did you exercise that care here
24 as it relates to the Buz'Zard study?

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1 A So the Buz'Zard study, you know,
2 primarily, as -- as referenced, was to illustrate
3 a study that showed an increase in reactive
4 oxygen species generation, and that's the -- the
5 primary purpose, or I should say primary
6 observation on the -- from this.

7 Now, certainly, the study contained
8 more observations than that and certainly had
9 some -- you know, a number of other components.

10 Q How does the Buz'Zard study support
11 your view that talcum powder causes chronic
12 inflammation that causes ovarian cancer?

13 A So the Buz'Zard study supports the view
14 that exposure to talcum powder causes an
15 inflammatory response.

16 Q And that inflammatory response you saw
17 in the Buz'Zard study does not increase with
18 increasing doses of talcum powder. Correct?

19 A I have to review. I believe that -- I
20 believe their figures suggest --

21 You know, are you referring
22 specifically to their reaction -- reactive oxygen
23 specie generation?

24 Q Correct.

1 MS. O'DELL:

2 Figure 3.

3 A Figure 3?

4 The one interesting observation in
5 these two figures, both Figure 3A and Figure 3B,
6 being the percentage of reactive oxygen specie
7 generation in two different cell types, one in --
8 one in Panel A and one in Panel B, is -- what I
9 did not see included, if I --

10 And I'm reading to see if I recall
11 correctly.

12 -- was a -- the -- the cell viability
13 assay that they use for normalization has
14 a -- somewhat of a limitation in that it -- it
15 doesn't measure cell senescence. It only
16 measures cell death. And, so, they -- not to
17 dis- -- not that I disagree with your observation
18 that it did not show the sig- -- significant
19 increase, but there is the possibility that the
20 reason that you see an actual decrease in the RS
21 generation at the higher doses of talc is that
22 cells have gone senescent and are essentially no
23 longer responding to that increased dose.

24 So I think there's at least two

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1 different ways to interpret some of these
2 results. But I don't disagree with your
3 observations regarding Figure 3.

4 MS. BROWN:

5 Q This study was conducted in a
6 nutritional lab, not a cancer lab. True?

7 A I'm -- I'm not aware of the type of
8 laboratory or even the...

9 Q And the study was -- the purpose of the
10 study was to assess whether there was a certain
11 effect of pine bark supplement? Is that right?

12 MS. O'DELL:

13 Objection to form.

14 A They were looking at the -- the effect
15 of a proprietary -- as stated by the authors, a
16 proprietary mixture of water soluble
17 bioflavonoids extracted from French maritime pine
18 bark.

19 MS. BROWN:

20 Q Uh-huh.

21 And did you investigate whether the
22 ovarian cells that they used here were
23 genetically altered?

24 A No, I did not investigate that.

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1 Q Did you --

2 I'm sorry. Were you done?

3 A No. I would say it's fair -- it's fair
4 to say that, you know, that the -- whether
5 they're genetically altered or not, the -- the --
6 you know, the same potential limitations as far
7 as extrapolation to the human system would apply
8 for any signs.

9 But, again, the purpose of the Buz'Zard
10 study, as -- as referenced in the report, was to
11 indicate that there are studies that have shown
12 an increase in reactive oxygen specie generation
13 under exposure to -- to talc. And I think the
14 study is reasonably clear on that increase
15 relative to control.

16 Q Except what this study showed, Doctor,
17 is the more talc you give, the decrease from
18 baseline in the reactive oxygen species.

19 Correct?

20 MS. O'DELL:

21 Object to the form. Asked and
22 answered. Misstates the testimony.

23 MS. BROWN:

24 Q Take a look at Figure 3; right, Doctor?

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1 A No. I agree. But, as stated, and an
2 important clarification is whether that decrease
3 is significant relative to the biology is -- is
4 unknown.

5 Q Right.

6 This study certainly does not
7 conclusively show that the more talc you give,
8 the more ROS is generated. Correct?

9 MS. O'DELL:

10 Object to the form.

11 A In these particular cell lines under
12 these conditions, the -- the study certainly did
13 not draw that conclusion.

14 MS. BROWN:

15 Q In fact, what this study shows is the
16 more talc you give, the less of -- of ROS
17 generation you have. Doesn't it?

18 MS. O'DELL:

19 Object to the form.

20 A I think importantly in this study, the
21 time dependency for each of the doses is more
22 important at the doses rather than comparing dose
23 to dose.

24 MS. BROWN:

1 Q My question was, Doctor, what this
2 study shows is the more talc you give, the less
3 ROS generation there is. True?

4 MS. O'DELL:

5 Objection to form.

6 A Again, under -- under the conditions of
7 this particular study.

8 MS. BROWN:

9 Q Do you think the Buz'Zard study is
10 scientifically reliable?

11 A I have no basis to -- to suggest that
12 it's -- that it's not reliable.

13 Q Do you think that --

14 A But I think there -- it does -- if
15 there is a -- as we discussed earlier, an
16 importance to not overgeneralize conclusions or
17 lack of conclusions as, you know, outside of the
18 system under study.

19 Q If -- I want you to assume that the
20 Buz'Zard study used genetically altered ovarian
21 cells that did not have the p53 protein. Would
22 that affect your analysis of Buz'Zard?

23 MS. O'DELL:

24 Object to the form.

1 A Well, that's -- that's an impossible
2 question. Like you can't have --

3 Well, you can't call a cell type a
4 normal ovarian cell and -- absent p53 protein.
5 You're -- it'd be -- you're fundamentally
6 changing the biology of the cell as it relates to
7 ovarian cancer or cancer in general.

8 MS. BROWN:

9 Q Because p53 is something that you have
10 in your genes that prevents against ovarian
11 cancer. True?

12 MS. O'DELL:

13 Objection.

14 A So p5- -- p53 is a well-known, often
15 mutated gene in a number of human cancers.

16 MS. BROWN:

17 Q And, so, if the ovarian cells that were
18 studied in Buz'Zard did not have p53, it will
19 call into question the study. Fair?

20 MS. O'DELL:

21 Object to the form.

22 A It would be difficult to answer. From
23 the perspective of the presence or absence
24 of -- of p53 having an effect on the ability of a

1 cell to generate reactive oxygen species under --
2 under exposure to a substance like talcum powder
3 would need to be tested directly.

4 MS. BROWN:

5 Q Fair to say, in your mind, a cell
6 missing p53 is not a normal human ovarian cell.
7 True?

8 A That is true.

9 (DEPOSITION EXHIBIT NUMBER 18
10 WAS MARKED FOR IDENTIFICATION.)

11 MS. BROWN:

12 Q Handing you what we've marked as
13 Exhibit 18 to your deposition, it's a review
14 article titled "Perineal Talc Use and Ovarian
15 Cancer," by Ross Penninkilampi.

16 Do you see that?

17 A I do.

18 Q This is an article that you cited in
19 your report; correct?

20 A Correct.

21 Q Does this article support your view
22 that there is a biolo -- in part --

23 Strike that.

24 Does this article, in part, support

1 your opinion in this case that there is a
2 biologically plausible mechanism by which talcum
3 powder can cause ovarian cancer which can
4 cause --

5 Strike that. Gonna do it again.

6 Does this article support your view, in
7 part, that talcum powder can cause chronic
8 inflammation that can cause ovarian cancer?

9 A This is an article I considered in
10 the -- in the overall review and, in the
11 conclusions of this article, found a -- an
12 association between perineal talc use and ovarian
13 cancer, according to the authors.

14 So it was supportive of the proposed
15 mechanism but was, again, in part.

16 Q And, on page 13 and 14 of your report,
17 you, in fact, reference the Penninkilampi study
18 and some of its conclusions; correct?

19 A Correct. On the -- on the bottom of
20 page 13, yes.

21 Q And what was the purpose of including
22 this description of Penninkilampi in your expert
23 report, Doctor?

24 A Just to be sure to be -- to include

1 available literature and, in this case, review a
2 meta-analysis of some reasonably large-scale
3 studies to try to bring the proposed biologically
4 plausible mechanism and include the -- the
5 available epidemiological information for those,
6 such as the Penninkilampi and Eslick paper we're
7 discussing.

8 Q What methodology did you employ in
9 terms of reviewing the Penninkilampi findings as
10 it relates to the question you addressed in your
11 report?

12 MS. O'DELL:

13 Object to the form.

14 A I -- I used the same methodology for
15 the other studies as a review of the paper and
16 its -- and its methods and conclusions.

17 MS. BROWN:

18 Q Do you believe this review, systematic
19 review and meta-analysis, provides evidence that
20 there's a biologically plausible mechanism by
21 which talc can cause ovarian cancer?

22 A Yes. It provided -- it shows an
23 association between talc use and ovarian cancer.
24 I don't -- I don't believe this particular study

1 goes on to specifically elucidate causation, but
2 it certainly shows the association.

3 Q Well, the study specifically says that
4 causation cannot be found, based on the results.
5 Right?

6 MS. O'DELL:

7 Objection to form.

8 MS. BROWN:

9 Q If you look at page 42, Doctor, the
10 very end of that first paragraph, "A certain
11 causal link between talc use and ovarian cancer
12 has not been established."

13 Do you see that?

14 MS. O'DELL:

15 Where are you? Page 42. Where are you
16 reading, please?

17 MS. BROWN:

18 Page 42, the end of the first
19 paragraph.

20 A Yes, I see that.

21 MS. BROWN:

22 Q Do you agree with that statement,
23 Doctor, that a causal link between talc use and
24 ovarian cancer has not yet been established?

1 MS. O'DELL:

2 Objection.

3 A No, I wouldn't. But, again, my review
4 of this was to tie the biologically plausible
5 mechanism to, you know, human observation, not
6 provide a evaluation of the -- of the causal
7 link.

8 And I think the -- I would suspect that
9 the --

10 I'm also not aware of a study that has
11 been able to -- or a -- or a -- what would be
12 necessary --

13 I'm not aware of a study that has been
14 able to provide all of the recognized and
15 established methodology for causation and have
16 that applied in -- in talc.

17 MS. BROWN:

18 Q You're not aware of any study in the
19 talc epidemiology that has concluded that talcum
20 powder causes ovarian cancer; correct?

21 MS. O'DELL:

22 Objection to form.

23 A I'm aware of a number of studies that
24 have shown a strong correlation between the two.

1 But I would have to defer to the epidemiology
2 expert witnesses as to their opinion on
3 causation.

4 MS. BROWN:

5 Q One of the things you told us that you
6 reviewed in connection with your opinion was the
7 talc epidemiology. Is that right?

8 A That's right.

9 Q Did you conduct a review of all of the
10 available epidemiology on talcum powder use and
11 ovarian cancer?

12 A I certainly tried to review it as
13 comprehensively as -- as possible.

14 Q And, in connection with that review,
15 you'll agree there is not a single study that
16 concludes there is a causal association between
17 talcum powder use and ovarian cancer; correct?

18 MS. O'DELL:

19 Objection to form.

20 A So I would -- I would -- interestingly,
21 there -- it's -- it becomes a -- as more -- as
22 more and more information has become available
23 over the last few years, that becomes a more and
24 more difficult bar to meet, simply because, to

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1 examine that comprehensively, when you consider
2 the etiology of a disease and the latency periods
3 that have been observed in ovarian cancer in
4 general and the meta review by both this earlier
5 paper by Penninkilampi and then their subsequent
6 later work, you have a challenge of a -- in a
7 cohort study, a disease that is somewhat rare,
8 coupled with a exposure and latency period that's
9 been, in the -- in the limited number of studies
10 that have looked at this, appears to be quite
11 long, and then when you couple in the -- the
12 ethical concerns of actually performing a trial,
13 where it becomes a very difficult causation bar
14 to reach.

15 And, so, instead, we rely on the
16 case -- the available case-control data and then
17 systematic and meta-analysis reviews such as some
18 of the epidemiologists have performed to make
19 assessments into the likelihood that -- and the
20 strength of the association between talc use and
21 ovarian cancer.

22 Q Are you intending to provide an opinion
23 on the strength of the association between talc
24 use and ovarian cancer as evidenced in the

1 epidemiology?

2 MS. O'DELL:

3 Object to the form.

4 A No. My -- my opinions are limited to
5 the biologically plausible mechanism and then
6 examining whether that biologically plausible
7 mechanism presented is supported by observations
8 in -- in available human studies.

9 MS. BROWN:

10 Q And when you say your opinion is
11 limited to a biological plausible mechanism, are
12 you talking of the theoretical concept or are you
13 talking about in the context of women using
14 talcum powder perineally?

15 A In the context --

16 MS. O'DELL:

17 Object to the form.

18 THE WITNESS:

19 Sorry.

20 MS. O'DELL:

21 Excuse me.

22 A In the -- in the context of women using
23 talcum powder perineally specifically, and
24 then -- and then certainly also the -- some of

1 the fundamental aspects of that mechanism may
2 apply to other exposures as well.

3 MS. BROWN:

4 Q Like what?

5 A Well, the -- the other exposure we've
6 been discussing, in -- in that some of the
7 studies looked at inhalation exposure, et cetera.

8 But the primary review and the primary
9 opinion is based on the perineal use of talcum
10 powder and that exposure that, as -- as we
11 discussed earlier, has a -- certainly a strong
12 association with perineal use and an exposure --
13 exposure in the ovaries.

14 Q Your opinion is that if a woman uses
15 talcum powder perineally, there is a biologically
16 plausible mechanism by which enough talcum powder
17 can migrate from outside of her vagina to her
18 ovary to cause chronic inflammation that can lead
19 to ovarian cancer?

20 MS. O'DELL:

21 Object to the form.

22 A So I'd say that the first part of your
23 question is well established and included in the
24 statements from FDA and others that that

1 migration does occur.

2 And then the next step in the -- in the
3 mechanism is that that causes inflammation which,
4 again, as we've discussed, in a number of
5 studies, that the inflammation occurs and then,
6 in these human studies, in their systematic
7 review, that there is a clear association or a --
8 a observed association between perineal use of
9 talc and the detection of ovarian cancer at some
10 point in the -- in the women's lives and, in the
11 case of the Penninkilampi, with a relationship to
12 the number of lifetime applications.

13 So considering those things together,
14 yes, there is a biologically plausible mechanism
15 for perineal talc use through to ovarian cancer.

16 MS. BROWN:

17 Q Have you -- is -- is your opinion that
18 there's a biologically plausible mechanism
19 dependent on a particular number of years of
20 perineal use?

21 MS. O'DELL:

22 Objection to form.

23 A The -- so the -- as we just discussed,
24 there's no -- I can't point to a formal clinical

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1 trial that would examine that in a well-powered
2 fashion to answer that question directly. And,
3 certainly, as of today, there would be some
4 significant ethical concerns with that design.

5 So, instead, we rely on the cohort and
6 case-control studies that are available. And
7 those, again, studies are supporting an
8 association between talc use and ovarian cancer.

9 MS. BROWN:

10 Q Right. But I'm talking about for your
11 opinion that it's biologically plausible for
12 perineal use of talc to cause ovarian cancer,
13 have you made a determination, in your mind, of
14 how long that perineal use has to take place for?

15 MS. O'DELL:

16 Object to the form.

17 A I wasn't asked to provide -- to provide
18 that opinion on -- and it -- on that length or
19 exposure or duration.

20 Again, it was -- the focus was on the
21 biologically plausible mechanism that if you have
22 a single exposure and that -- that that single
23 exposure through to any other may be sufficient
24 to trigger that mechanism.

1 MS. BROWN:

2 Q That's helpful, Doctor.

3 So, as I understand your opinion, your
4 piece of the puzzle here was to look at whether
5 one single application of talcum powder to the
6 perineum could lead to chronic inflammation that
7 could cause ovarian cancer.

8 MS. O'DELL:

9 Objection.

10 MS. BROWN:

11 Q Correct?

12 A No, no.

13 MS. O'DELL:

14 Object to the form of the question.

15 A No. That's not my -- my statement.

16 My statement was that, based on the
17 evidence available, that there's a biologically
18 plausible mechanism for the -- for the cellular
19 changes that -- that is independent of the
20 exposure.

21 MS. BROWN:

22 Q You've made a determin- --

23 A But certainly a single exposure would
24 be the physically minimum number. And I

1 believe -- I think we --

2 Q That's what I want to understand. And
3 how you -- how you make this biological
4 plausibility determination is to evaluate a
5 single exposure? Is that right?

6 MS. O'DELL:

7 Object to the form.

8 A No.

9 MS. O'DELL:

10 Misstates his testimony.

11 A That's -- that's not what I'm stating.

12 My -- my statement is that the -- the
13 biologically plausible mechanism is a mechanism
14 that is independent of the exposure and that, as
15 part of the description of that mechanism and the
16 evaluation of the studies supporting that
17 mechanism through an inflammatory response, the
18 question of exposure, number, and duration,
19 length of time, et cetera, would be a separate
20 evaluation.

21 MS. BROWN:

22 Q Is your opinion that talcum powder
23 products cause chronic inflammation that cause
24 ovarian cancer limited to perineal use, or have

1 you also evaluated body use of talcum powder
2 products?

3 MS. O'DELL:

4 Object to the form.

5 A My -- my focus was on the perineal use,
6 and that's where the majority of the studies
7 have -- have examined. So the focus was on
8 perineal use of talcum powder.

9 MS. BROWN:

10 Q And in conducting that evaluation, the
11 results of which are contained in your report,
12 you did not endeavor to quantify how much talcum
13 powder used perineally could possibly migrate to
14 the ovaries; is that right?

15 MS. O'DELL:

16 Object to the form. Asked and answered
17 maybe ten times already today.

18 But you may answer the question.

19 A Yeah. I -- I wasn't asked to -- to
20 provide that opinion or attempt that
21 quantitation.

22 MS. BROWN:

23 Q So when you conduct your analysis of
24 whether something can biologically cause an

1 effect, it doesn't matter at all how much of the
2 product is used?

3 MS. O'DELL:

4 Objection.

5 MS. BROWN:

6 Q Do you see what I'm struggling with?
7 Can you help me understand? If I'm trying to
8 figure out does X cause Y, it sounds like what
9 you're saying is it doesn't matter how much X you
10 have.

11 MS. O'DELL:

12 Objection to form.

13 A So we're -- we're talking about
14 mech- -- so mechanistic action --

15 MS. BROWN:

16 Q Okay.

17 A -- which means the -- you set aside the
18 "how much." And the question is, from -- on a
19 molecular level, can the presence of a particular
20 compound in a particular location cause a
21 biological effect. And, so, that is the primary
22 focus of the opinion in the -- in the paper or --
23 sorry -- in my report.

24 And then extending that to how much,

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1 how long, and the dur- -- and then the intensity
2 or duration of the biological effect, again, is a
3 separate -- would be a separate discussion or
4 separate study.

5 So, again, to clarify, the focus had
6 been on that -- some of the fundamental
7 mechanisms, talc -- a talcum powder exposure to
8 an inflammatory response to the inflammatory
9 response causing cancer.

10 Again, the -- I would refer to and
11 defer to the other experts in epidemiology
12 regarding their opinions on the validity of
13 the asso- -- validity and strength of the
14 associations, again, from a formal epidemiology
15 perspective.

16 My review of those studies has ind- --
17 has relied on their conclusions, and, then, in my
18 own review of their -- of their methodology
19 showing a increasing association, that is the
20 bookends of my -- of the mechanism I proposed.

21 So what this study is looking at is
22 perineal use of talc, getting cancer.

23 The -- what I've proposed is in the
24 middle. But this, again, the epidemiology

1 studies are asking how many times, what, and
2 where, but there's been no evaluation that I'm
3 aware of that looks at exactly how the talc was
4 applied, when and where. Instead, it was asked
5 number of lifetime applications, duration of use,
6 and examining latency period.

7 And when I examine that information
8 from the perspective of that biological
9 mechanism, I, you know, notice some parallels in
10 between latency period averaging roughly twenty
11 years, which -- which mimics somewhat what's
12 observed in the asbestos field as far as, you
13 know, lung effect latency.

14 And then that continues into the
15 constituent -- or the other constituent
16 components of some of the products, including
17 testing into asbestos and some of the -- and
18 heavy metal exposure, et cetera, that those are,
19 again, supportive and offer a potential
20 amplifying effect in that -- in that mechanism,
21 given the nature of those other components.

22 Q What's the scientific support for the
23 amplification effect you just described?

24 A Just that the presence of

1 more -- the --

2 So if we extend beyond the opinion that
3 talc, as a com- -- as a singular compound, causes
4 inflammation and then also, based on the reviewed
5 expert reports, find that testing of talc has
6 been shown to contain asbestos or asbestos
7 fibers, that the presence of now two potential
8 insulting --

9 I'm making a hypothesis or making a
10 statement that the -- you can have -- the more
11 biologically active compounds you have in an
12 exposure such as talc plus asbestos plus chromium
13 and then plus a milieu of chemicals that are in
14 fragrances may have an amplification effect on
15 that exposure and as part of that overall
16 biological mechanism.

17 Q Are you relying on a particular article
18 or any published scientific support for the
19 amplification argument?

20 MS. O'DELL:

21 Object to the form. He's answered the
22 question.

23 A No. I -- I don't know of a study that
24 is delineated. The -- it would be synthesizing

1 that opinion from the observations of a couple of
2 different studies, including the recent Saed
3 paper that did look at the specific consumer
4 product every -- you know, showing a -- if we do
5 it by way of comparison, between the Buz'Zard
6 paper and the recent Saed, seemingly a larger
7 magnitude of reactive oxygen species generation.
8 But, again, that is a -- extrapolating against
9 two different studies.

10 Q Do you --

11 MS. O'DELL:

12 Excuse me. We've been going about an
13 hour and 20 minutes, maybe a little more.

14 MS. BROWN:

15 I think a little less. But I'm gonna
16 finish up. Then we'll take a quick break.

17 Q Does that work for you, Doctor?

18 I just want to finish Penninkilampi if
19 we can.

20 MS. O'DELL:

21 How much more do you have to go?

22 MS. BROWN:

23 About five or ten minutes.

24 MS. O'DELL:

1 discussion that begins on page 45. In the second
2 sentence, the authors conclude here that the
3 mechanism by which perineal talc use may increase
4 the risk of ovarian cancer is uncertain.

5 Do you see that?

6 A I see that sentence, yes.

7 Q And they go on to discuss the theory
8 that talc could produce a chronic inflammatory
9 response which could predispose to the
10 development of ovarian cancer.

11 Do you see that?

12 A Yes.

13 Q Okay. And they go on to explain a
14 little bit more about the theory. Do you see
15 that?

16 MS. O'DELL:

17 Object to the form.

18 A Specifically the sentence beginning
19 with "it is argued"?

20 MS. BROWN:

21 Q Uh-huh. "It is argued that cellular
22 injury, oxidative stress, and local increase in
23 inflammatory mediators such as cytokines,
24 prostaglandins may be mutagenic and, hence,

1 promote carcinogenesis."

2 Do you see that?

3 A I see that.

4 Q This sentence refers to chronic
5 inflammation promoting cancer. Correct?

6 MS. O'DELL:

7 Object to the form.

8 A No. This -- this refers to that the
9 presence of -- proposed that talc as a
10 foreign -- that the presence of a foreign body
11 would instigate a chronic inflammatory response.
12 That's the statement in the paper.

13 MS. BROWN:

14 Q Is it your opinion that talcum powder
15 can cause chronic inflammation that initiates
16 cancer?

17 A It's -- so it is -- it is my opinion
18 is, part of the mechanism, that talcum powder can
19 have two effects related to inflammation. The
20 first effect is an acute effect resulting in
21 cellular damage, and that is supported by the
22 study showing increase in reactive oxygen species
23 related to talc.

24 The -- beyond that, the continued

1 presence of the talc or a continued chronic
2 immune response or chronic inflammatory response,
3 again, either directly or indirectly related to
4 the exposure, would help support a environment
5 that would allow the cancer progression to occur.

6 So that is simply delineating those --
7 those two things as it relates to inflammation
8 and talc exposure.

9 Q So you described two potential
10 responses to talc right now. Correct?

11 MS. O'DELL:

12 Objection to form.

13 A At least two, yes.

14 MS. BROWN:

15 Q Okay. And one is an acute inflammatory
16 response; correct?

17 A Yes.

18 Q And for that you point to the Saed data
19 on reactive oxygen species; is that right?

20 MS. O'DELL:

21 Objection to form.

22 A That is one example, yes.

23 MS. BROWN:

24 Q Okay. Are there -- is there other

1 scientific support for your opinion that talc can
2 cause acute inflammation?

3 A So it's any of the similar studies to
4 Saed. And I would have to double-check the
5 references, but they would have -- you know, any
6 of the --

7 MS. O'DELL:

8 Feel free to --

9 MS. BROWN:

10 Q Buz'Zard?

11 A So Buz'Zard would be one. Harper and
12 Saed is -- is another.

13 Q In your --

14 A And so -- yeah. Yes, Buz'Zard and Lau
15 and then -- yeah. So that would --

16 Q Okay. So for your opinion that talc
17 causes an acute inflamm- -- inflammatory
18 response, you rely on the cell studies done by
19 Saed and Buz'Zard; correct?

20 MS. O'DELL:

21 Object to the form.

22 A Yes, among others.

23 MS. BROWN:

24 Q In your opinion, Doctor, does that

1 acute inflammatory response resolve?

2 A I don't -- I don't have any evidence to
3 suggest it resolves or not. The --

4 Again, getting back to the mechanism
5 that has been -- that I've described and is
6 supported by the literature we've been discussing
7 is that there is a acute response as well as
8 evidence for talc causing a more chronic
9 inflammatory response. And so I've proposed a
10 mechanism by which both of those can contribute
11 to or enhance the development of cancer.

12 Q Can both of those inflammatory
13 responses that you just described initiate
14 cancer?

15 MS. O'DELL:

16 Object to the form. Asked and
17 answered.

18 A They are certainly a component of that.

19 And so, again, to restate the
20 mechanism, the acute inflammatory response or
21 the -- the formation of reactive oxygen species
22 has been known for decades to cause cellular
23 damage, and then cellular damage can result in
24 mutation of -- of DNA.

1 And then when you also consider the
2 full constituents of the products, the potential
3 presence --

4 And this gets back to our earlier
5 discussions about amplification.

6 Components such as chromium, which have
7 a direct DNA-damaging effect, can also
8 ampli- -- again, add to the level of cellular
9 damage present.

10 And then the continued inflammatory
11 response, whether it is a -- related to the
12 initial acute response and a continuation of that
13 or is a separate chronic inflammatory response
14 would then support the environment necessary for
15 the malignant transformation or the malignancy of
16 the cancer to become what we -- what we would
17 generally refer to as ovarian cancer.

18 Q In your opinion, the chronic
19 inflammation promotes the cancer but does not
20 initiate it?

21 MS. O'DELL:

22 Object to the form. Asked and
23 answered.

24 A No. So I wouldn't -- I would say

1 they're not -- I don't have evidence to -- to
2 delineate those specifically, other than -- other
3 than the supported mechanism that an acute
4 response can cause cellular damage, and then a
5 chronic response can cause cellular damage and be
6 supportive of that continued -- that continued
7 transformation.

8 So they are -- they -- those -- those
9 two delineated immune responses can either work
10 in -- in concert with each other, but there is no
11 evidence to suggest that one is insufficient
12 relative to the other in terms of progression of
13 the disease.

14 And I think specific to the -- to the
15 supported mechanism is that there -- I'm not
16 making that distinction in the -- in the report.

17 MS. BROWN:

18 Q Right. In your report, you don't talk
19 about acute versus chronic inflammation.

20 Correct?

21 A That's correct. I don't delineate the
22 two. Right.

23 Q But, here today, as we discuss in more
24 detail your opinions, you're explaining that

1 you're -- in your mind, you see two potential
2 inflammatory responses from talc. Right?

3 MS. O'DELL:

4 Object to the form.

5 A I would disagree. I would say that
6 I -- I -- based on the information and studies,
7 the -- the review of other expert reports, that
8 it presents a supported opinion that talc has an
9 ability to cause an acute response as well as a
10 chronic response.

11 And, so, then, today we are discussing
12 using that data in support of the -- of the
13 mechanism as to how those -- those two responses
14 can work together or separately in the
15 progression of ovarian cancer.

16 MS. BROWN:

17 Q At the time you wrote your report in
18 November of 2018, were you of the view that talc
19 can cause both acute and chronic inflammatory
20 response?

21 A Yes. I mean, it was -- I was of the
22 view it causes an inflammatory response. And
23 then, as I continued to review information
24 available, it became clear that the talc

1 response, being an inflammatory response in
2 totality, may have the ability to have
3 those -- to -- to have two independent responses
4 in tissues.

5 Q And, in your opinion, can both the
6 acute inflammatory response and the chronic
7 inflammatory response separately cause ovarian
8 cancer?

9 A Under the -- the mechanism I've
10 proposed, yes, that would be a -- a possibility
11 that they could separately cause, given that
12 they -- they're both inflammatory responses, they
13 both cause cellular damage.

14 And in the case -- in this case,
15 delineating the acute from chronic was more to
16 clarify the cellular damage aspect, the
17 transformative aspect of cancer from the -- the
18 necessary tumor progression aspects of cancer to
19 actually progress to disease.

20 Q In your opinion, Doctor, does talc
21 always first cause an acute reaction and then a
22 chronic reaction?

23 MS. O'DELL:

24 Object to the form.

1 A I -- I -- I don't have evidence
2 to -- to state that and would defer to some of
3 the other expert witnesses, like Dr. Saed, for
4 opinions on acute response versus chronic.

5 MS. BROWN:

6 Q In your opinion, though, you have at
7 least delineated in your mind two different types
8 of inflammatory responses. Correct?

9 MS. O'DELL:

10 Objection to form.

11 A I've -- I have described two mechanisms
12 for inflammation that -- that both can -- are
13 both supportive of the overall mechanism that
14 we're discussing.

15 MS. BROWN:

16 Q And is it -- is there a length of time
17 that differentiates an acute inflammatory
18 response from a chronic inflammatory response?

19 A Certainly I would say there -- in my
20 opinion, there would -- it would be a potential
21 time dependency or a magnitude dependency to
22 delineate an acute versus chronic response. But,
23 again, for the purpose of the biological
24 mechanism, separating them on those lines is not

1 important.

2 Q So there is a length of time or an
3 amount of exposure that would cause a chronic
4 inflammation that is different from the length of
5 time and the magnitude of exposure that will
6 cause an acute inflammation?

7 MS. O'DELL:

8 Object to the form. Misstates his
9 testimony.

10 A Yeah, no. Not -- that's not what
11 I -- that's not what I've stated.

12 I've simply stated that if we -- if we
13 look at the -- what is known about inflammation
14 and the biological response to foreign bodies,
15 you can have an initial acute response mediated
16 by the immune system and mediated by some of the
17 cellular damage that takes place, and then that
18 same response may continue in a chronic form for
19 some period of time and at some level of
20 magnitude.

21 Now, certainly there is likely a
22 dependency or, I should say, likely a
23 relationship to the amount of exposure and the
24 magnitude of that response.

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1 But, again, the -- the opinions here
2 are specific to the mechanism and the initial
3 elucidation of that response and, you know,
4 not -- not on a quantitation of a -- a
5 dose-response relation -- or a dose-response
6 curve or relationship.

7 MS. BROWN:

8 Q Do you believe that every time a talc
9 particle enters the human body, it produces a
10 inflammatory response?

11 A All of the evidence would suggest yes.

12 Q Have you considered Heller's 1996 study
13 on that score?

14 A I would have to --
15 On the score of inflammatory response?

16 Q Do you recall that Heller looked at
17 benign ovarian tissue and identified the
18 potential presence of talc?

19 A Sounds familiar.

20 Q I'll hand it to you.

21 (DEPOSITION EXHIBIT NUMBER 19
22 WAS MARKED FOR IDENTIFICATION.)

23 MS. BROWN:

24 Q Handing you, Doctor, what we've marked

1 Heller's '96 article as Exhibit 19.

2 And what I want to ask you about is
3 Heller's finding as it relates to no reaction to
4 the talc particle. Did you consider that --

5 MS. O'DELL:

6 Object to the form.

7 MS. BROWN:

8 Q -- in forming your opinion here?

9 MS. O'DELL:

10 Excuse me. Object to the form.

11 MS. BROWN:

12 Q I'll direct you, Doctor.

13 On page 1508 of the Heller article,
14 right above the comments section, "The
15 investigators on this study concluded no evidence
16 or response to talc, such as foreign body giant
17 cell reactions or fibrosis in the tissue."

18 My question is whether, in your
19 opinion, every time talc is -- enters the body,
20 it necessarily produces an inflammatory response.

21 MS. O'DELL:

22 Object to the form.

23 A No. My opinion is that every time talc
24 enters the body, that has the potential to cause

1 an immune response.

2 MS. BROWN:

3 Q Have you made a determination about
4 whether or not that always happens?

5 A I'll have --

6 MS. O'DELL:

7 Object to the form. It's vague.

8 A I'm not aware of any --

9 There -- there -- these -- none of the
10 studies that have been reviewed have been
11 designed to answer the question of "if ever."

12 MS. BROWN:

13 Q So, in your view, then, it's an open
14 question about whether talc can be inside the
15 body and not produce an inflammatory response.

16 MS. O'DELL:

17 Object.

18 MS. BROWN:

19 Q Is that fair?

20 MS. O'DELL:

21 Excuse me. Objection to form.

22 Misstates his testimony.

23 A So my -- my -- my testimony regarding
24 the mechanism is that there is a well-supported

1 mechanism that talc causes inflammation and then
2 inflammation has a role in ovarian cancer.

3 Extending that to circumstances where
4 an exposure would not cause inflammation is -- is
5 not germane to that -- to that mechanism and, in
6 fact, again, not supported by literature to show
7 that, you know, that a single exposure or some
8 number of exposures are necessary or sufficient
9 for a particular phenotype.

10 MS. BROWN:

11 Q So this Heller study purports to have
12 found talc in ovarian tissue without an
13 inflammatory response; right?

14 MS. O'DELL:

15 Object to the form.

16 A In looking at their --

17 Just one moment.

18 So this was a --

19 So is your -- is your question that
20 the -- if the -- if the author showed talc being
21 present in normal ovarian tissue?

22 Q Well, first my question is did you
23 consider this article in connection with your
24 opinions in the case?

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1 A I don't recall this article
2 specifically, and I don't believe I cited it.

3 I guess there's -- no.

4 Q And then my second question, Doctor, is
5 is it your opinion that every time the human body
6 is exposed to particles of talc, it necessarily
7 produces an inflammatory response that can either
8 promote or initiate cancer of the ovaries?

9 MS. O'DELL:

10 Object to the form.

11 A No. My --

12 MS. O'DELL:

13 Vague.

14 A My comment was that the -- that any
15 exposure to talc, particularly the perineal
16 exposure to talc, has the potential to cause an
17 inflammatory reaction.

18 I don't have any evidence that all of
19 the studies that we've been reviewing are in
20 support -- are in support of that mechanism, but
21 I don't know of a study that perhaps has been
22 able to draw a conclusion, from a similar size
23 study, to show that you can get significant talc
24 accumulation without an inflammatory response.

1 MS. BROWN:

2 Q Do you think you need significant talc
3 accumulation in the human body to cause or
4 promote ovarian cancer?

5 MS. O'DELL:

6 Objection to form.

7 A I wasn't asked to -- to provide --
8 provide that opinion.

9 And, again, referring to the studies
10 that have -- that were reviewed and included in
11 the report, there is a relationship between
12 lifetime exposure and an increased risk in the
13 epidemiology reports.

14 But more detail on that in this
15 discussion, I would defer to the epidemiology
16 experts. But the -- there -- there does appear
17 to be a -- more of a response based on more talc
18 in the -- in the studies referenced.

19 MS. BROWN:

20 Q So on --

21 Do you have any reason to dispute the
22 findings of Heller here of talc in the ovaries
23 without a foreign body reaction?

24 MS. O'DELL:

1 Objection.

2 A I guess my -- I have some -- I guess I
3 have some concerns with some of the methodology
4 as it relates to the detection of the...

5 MS. BROWN:

6 Q Do you think it's possible, Doctor, for
7 talc to enter the body and -- and be completely
8 inert and not cause any reaction?

9 MS. O'DELL:

10 Object to the form.

11 A So my -- the -- the mechanism I've
12 proposed is -- is based -- you know, based on the
13 literature, is that talc causes an inflammatory
14 response and that inflammatory response is
15 supportive of progression to ovarian cancer.

16 MS. BROWN:

17 Q Does that happen 100 percent of the
18 time?

19 MS. O'DELL:

20 Object to the form. In terms of
21 inflammatory response or in terms of cancer?

22 MS. BROWN:

23 Q If you don't understand the question,
24 you'll let me know.

1 A In -- in terms of cancer, the
2 epidemiology would suggest -- or I would say
3 the -- the evidence in the literature is -- does
4 not allow that question to be answered, and the
5 reason being is when you look at the latency of
6 the disease and the progression of the disease
7 and the challenges in detecting it, there just
8 has not been enough time with the, perhaps, rigor
9 of analysis that is undergoing now to make that
10 assessment of is it 100 percent of the time or is
11 it something less than 100 percent of the time.

12 I think, statistically speaking,
13 there -- the only data that -- that is available
14 for review is -- is what is contained in some of
15 the meta-analysis and epidemiology studies
16 showing a significant increased risk to ovarian
17 cancer based on exposure to talc. And it
18 would -- it would only be -- I think it would be
19 inappropriate at this time to try to infer what
20 percentage of time that would be indicative of
21 for exposure.

22 Q Have the plaintiffs' lawyers shared
23 with you expert reports from their expert
24 pathologists who have looked at ovarian tissue of

1 plaintiffs in this litigation, purported to find
2 talc with no foreign body reaction?

3 MS. O'DELL:

4 Objection. There have been no
5 case-specific pathology reports disclosed in the
6 litigation we're here about today. And if
7 there's something else you're talking about, you
8 should be specific.

9 A The -- I don't recall a pathology
10 report. I've seen expert reports from
11 epidemiologists, OB-GYN and -- and some -- and
12 other scientists. But I don't recall a specific
13 pathology report.

14 MS. BROWN:

15 Q If the biologically plausible mechanism
16 that you posit in your report is true, would you
17 expect that the pathology slides of women with
18 ovarian cancer who have used talc would evidence
19 talcum powder with a foreign body reaction?

20 MS. O'DELL:

21 Object to the form. Incomplete
22 hypothetical.

23 A That, I would have to ask how you're
24 defining a foreign body reaction.

1 MS. BROWN:

2 Q Well, would you expect to see some
3 evidence of inflammation in the ovarian tissue of
4 women who used talcum powder products?

5 MS. O'DELL:

6 Object to the form. Incomplete
7 hypothetical.

8 A Overall, speaking to, as we were
9 discussing earlier, the potential for that
10 inflammatory response remains. But given the
11 heterogeneity in individuals, their overall
12 health, their natural variation in the levels of
13 activities of antioxidants, et cetera, I -- I
14 would state that I would expect a variety of
15 magnitude of response to a foreign body like talc
16 among the individuals exposed to it.

17 MS. BROWN:

18 Q You'd expect to see something; right?

19 MS. O'DELL:

20 Object to the form.

21 A No, not necessarily, because it -- it
22 very much depends on the timing that's -- that is
23 observed, how -- what methodology is used to
24 detect the presence of talc or detect the

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1 presence of the inflammatory response, if it's,
2 you know, done histopathologically, if it is
3 based on a reactive oxygen species assay.

4 So given the -- speaking in general
5 terms, I think it's just inappropriate to make a
6 conclusion as to that, yes, you would always
7 expect to see something.

8 I would -- again, to restate what was
9 stated earlier, any -- any exposure has the
10 potential to cause that inflammatory response,
11 and then the time, scale, and magnitude of that
12 response is going to vary by person. Therefore,
13 I would expect there would be a variability in
14 individuals exposed to talc.

15 MS. BROWN:

16 Q Uh-huh. Is your opinion related to all
17 the different histologic types of epithelial
18 ovarian cancer?

19 A My -- my opinion is not exclusive to
20 any -- any one type. Certainly, the epithelial
21 serous being the more common and most virulent
22 type of cancers I think represents the most
23 common.

24 From a mechanistic perspective, I

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1 mentioned some of the other subtypes and the
2 common gene mutations that go along with them and
3 as, again, supportive of the same mechanism. And
4 I think, if anything, the -- the current data
5 would suggest a -- a higher prevalence of a
6 particular subtype of cancer but certainly not
7 the -- the mechanism doesn't -- is not exclusive
8 to any one type.

9 Q In your view, all types of epithelial
10 ovarian cancer can be caused by inflammation?

11 A No. That's -- that's not my statement.
12 I would say all types of ovarian cancer are
13 supported by an inflammatory response but that,
14 as from a causative perspective, that's not what
15 the mechanism is provided as an opinion as to
16 cause. It's more that the -- an inflammatory
17 response plays a role in disease initiation
18 and/or progression.

19 Q In your view, Dr. Levy, it is
20 biologically plausible for inflammation to cause
21 all types of epithelial ovarian cancer; true?

22 A Again, I'm not -- I've not been
23 speaking to inflammation as a causative -- as a
24 cause of ovarian cancer. It is a factor in --

1 in -- in disease progression.

2 Q So when you conclude, as you do in your
3 report, that talcum powder products cause chronic
4 inflammation, you do not conclude that that
5 chronic inflammation causes ovarian cancer?

6 MS. O'DELL:

7 Object to the form.

8 A I wasn't asked to provide a causation.

9 MS. BROWN:

10 Q Your opinion here is limited to the
11 potential for talcum powder products to produce
12 inflammation; correct?

13 MS. O'DELL:

14 Object to the form.

15 A No. My -- so my opinion is a -- is a
16 supported plausible biological mechanism by which
17 the exposure to talc can lead to ovarian cancer.
18 And, in my opinion, as supported in the -- in the
19 report, that is through an inflammatory response.

20 MS. BROWN:

21 Q I must be missing you, Doctor. So are
22 you of the opinion that inflammation can cause
23 ovarian cancer?

24 A I'm of the opinion that inflammation is

1 a component of ovarian cancer.

2 Q Well, I'm not sure what you mean by
3 that. Can inflammation cause ovarian cancer?

4 MS. O'DELL:

5 Object to the form. Asked and
6 answered.

7 A I'm asked -- I suppose -- again, the
8 opinion here is of a mechanistic opinion, not a
9 causation. I would defer to some of the
10 epidemiology experts to have opinions on
11 causation.

12 MS. BROWN:

13 Q You don't have an opinion on whether or
14 not inflammation can cause ovarian cancer?

15 MS. O'DELL:

16 Different question.

17 A Correct. That's a --

18 As we've been discussing, my opinions
19 are that inflammation is a component of ovarian
20 cancer and can be attributed to aspects, not
21 exclusively, but contributing to aspects of its
22 initiation and aspects of its progression. But I
23 did not say that ovarian cancer is caused by
24 inflammation.

1 MS. BROWN:

2 Q And what scientific support do you have
3 for your opinion that inflammation is a component
4 of ovarian cancer and can be attributed to
5 aspects of ovarian cancer, including its
6 initiation?

7 A So, again, the synthesis of the -- of
8 the papers we've been discussing, including Saed
9 and others, showing the reactive oxygen species
10 produced from talc. And, then, as far as
11 inflammation and its role in cancer, there
12 are -- and it's a fundamentally accepted aspect
13 of cancer biology that's been around for -- for
14 quite some time. And we mentioned earlier that
15 there's a variety of review articles, including
16 the ones we were comparing sentences to earlier
17 today, that describe that in great detail.

18 Q It's not generally accepted, though,
19 that ovarian cancer is caused by inflammation.
20 Fair?

21 MS. O'DELL:

22 Object to the form.

23 A I think there's a number of studies
24 that --

1 Well, first, we're -- I want to be
2 cautious with our use of the word "cause"
3 and -- because that's, as we've been discussing,
4 this is a -- it is -- it is not controversial
5 that ovarian cancer -- inflammation plays a role
6 in ovarian cancer and -- and, again, my opinion
7 is not towards causation.

8 MS. BROWN:

9 Q Well, I mean, tumors themselves elicit
10 inflammatory responses; right?

11 A What -- so what -- specifically, what
12 are you referring to?

13 Q Well, you talk about tumor-activated
14 macrophages in your report; right?

15 A Yes.

16 Q There is an inflammatory response
17 that's produced by the tumor itself; correct?

18 A Yes. There are -- there -- there --
19 there are absolutely cancer progression markers
20 that are associated with continued inflammation.

21 Q And that has nothing to do necessarily
22 with the events that cause the cancer. Right?

23 MS. O'DELL:

24 Object to the form.

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1 A Well, so the -- we -- we would be going
2 down a slightly different road. And if
3 we're -- so cancer as a complex disorder, you
4 know, begins with an initiating event. But there
5 is -- there is absolutely tumor evolution from
6 that initial event through the progression of the
7 disease.

8 So to state that the -- in the initial
9 inflammatory response to the tumor is -- is not
10 causative to the continuation of the disease I
11 think would be incorrect.

12 MS. BROWN:

13 Q The Penninkilampi authors -- to
14 conclude our discussion here -- concluded that
15 the paragraph you were looking at with the
16 sentence "The potential mechanism by which
17 genital talc is associated with an increased risk
18 of ovarian cancer, hence, remains unclear," do
19 you see that?

20 A Yes.

21 Q And this meta-analysis was published in
22 January of 2018; correct?

23 A Correct.

24 Q And it is, in fact, cited in the

1 majority of the plaintiff expert reports in this
2 litigation. Did you see that?

3 MS. O'DELL:

4 Object to the form. If you know that.
5 Don't speculate.

6 MS. BROWN:

7 Q That's why I asked "Did you see that?"

8 A So I didn't specifically look at if
9 this was referenced. I -- I certainly referenced
10 it. But I would also point out another important
11 part of the -- of this same reference, a -- about
12 halfway down the following paragraph, beginning
13 with "If chronic inflammation due to ascending
14 foreign bodies is indeed the mechanism by which
15 talc use is associated with ovarian cancer risks,
16 then these results fit the picture."

17 So I think the authors were both
18 describing some things that remain unclear but
19 also offering some comments that are supportive
20 of our earlier discussions today on this
21 mechanism.

22 Q And your opinion here today, Doctor, is
23 limited to the potential mechanism; right?

24 MS. O'DELL:

1 Object to the form.

2 A So my -- my opinion is -- is -- is
3 regarding a biologically plausible mechanism.

4 But, then -- and, in doing so, have reviewed some
5 of these studies that we're discussing now.

6 MS. BROWN:

7 Q Good.

8 And, as it relates to that potential
9 mechanism, these Penninkilampi authors conclude
10 that the potential mechanism remains unclear.

11 Right?

12 MS. O'DELL:

13 Objection to form.

14 A They -- the article makes a statement,
15 "The potential mechanism by which genital talc is
16 associated with an increased risk of ovarian
17 cancer, hence, remains unclear."

18 However, as we've been discussing, they
19 go on to state, "If chronic inflammation due to
20 ascending foreign body is indeed the mechanism,"
21 then there -- the results in this paper
22 are -- fit that model.

23 So I think they're making reason- --
24 making reasonable statements based on the

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1 available data that there is a biologically
2 plausible mechanism surrounding and, indeed, in
3 the previous paragraph at the end of it where
4 they discuss use of -- or expression of
5 cyclooxygenase 1 and 2 as well as the action of
6 NSAIDs, again, supportive of -- somewhat
7 supportive of the inflammatory model. But...

8 MS. BROWN:

9 Q Well, as it relates to the NSAIDs,
10 Doctor, they point to the fact that the NSAID
11 data is inconsistent, at best, as evidence
12 supportive of their conclusions that the
13 mechanism is unclear; right?

14 A No. They point to it as -- they
15 actually try to clarify that the -- the seemingly
16 contradictory data regarding the NSAID use can be
17 explained by the relatively low expression of
18 cyclooxygenase 1 and cyclooxygenase 2, which are
19 the targets of most common NSAIDs.

20 Q What they say is that the use of
21 nonsteroidal anti-inflammatory drugs, NSAIDs, is
22 not inversely associated with the incidence of
23 ovarian cancer as may be expected if the etiology
24 was related to chronic inflammation. Right?

1 MS. O'DELL:

2 Objection to form.

3 A Yes, that statement is made. But,
4 importantly, it is incomplete without the next
5 sentence, again, explaining that -- that
6 apparent -- that apparent question.

7 So if the -- if NSAIDs are not
8 effective in ovarian cancer and the -- and, in
9 turn -- and if the observation is also made that
10 ovarian cancer cells don't express cyclooxygenase
11 1 and 2, then they would not -- they would be
12 nonresponsive to NSAIDs.

13 Q You state on page 12 of your report,
14 Doctor, in the last paragraph, the second-to-last
15 sentence that begins "moreover," that the effect
16 of nonsteroidal anti-inflammatory drugs, NSAIDs,
17 to reduce the risk of ovarian cancer provides
18 additional support for what you're discussing
19 here, which is that chronic inflammation plays a
20 key role in the development of ovarian cancer.

21 Right?

22 A Correct.

23 Q And that is, in fact, the opposite of
24 what the authors in Penninkilampi report as

1 relates to NSAIDs; right?

2 MS. O'DELL:

3 Object to the form.

4 A Not -- not necessarily. So there's --
5 getting back to the -- the specific cells under
6 question and the inflammatory response being
7 examined. And, so, if we are lowering overall
8 chronic inflammation through the use of an NSAID
9 is -- is one question. A separate question is is
10 a -- is a ovarian cancer cell responsive to
11 NSAIDs. So they're two separate biological
12 phenomenon.

13 And, in one case, if those cells are
14 not expressing the cyclooxygenase 1 and 2,
15 they'll be nonresponsive.

16 I would speculate that NSAID use in the
17 rest of the body would still result in the
18 expected effect due to, you know, the -- due to
19 the inhibition of cyclooxygenase 1 and 2.

20 So I don't think they're necessarily in
21 conflict with each other.

22 (DEPOSITION EXHIBIT NUMBER 20

23 WAS MARKED FOR IDENTIFICATION.)

24 MS. BROWN:

1 Q Handing you what we've marked as
2 Defense Exhibit 20 to your deposition, this is a
3 paper by Merritt entitled "Talcum Powder Chronic
4 Pelvic Inflammation and NSAIDs in Relation to the
5 Risk of Epithelial Ovarian Cancer."

6 Do you see that?

7 A I do.

8 Q And, in fact, on page 12 of your
9 report, you cite this Merritt article. Correct?

10 A Yes. Uh-huh.

11 Q And you cite it for the proposition
12 that studies have found a relationship between
13 pelvic inflammatory disease and ovarian cancer
14 risk. Correct?

15 A Correct.

16 MS. O'DELL:

17 Object to the form.

18 MS. BROWN:

19 Q And you point to Merritt when you
20 determine here as a finding of a relationship
21 between pelvic inflammatory disease and ovarian
22 cancer in support of your opinion that
23 inflammation can cause ovarian cancer. True?

24 A I'd have to double-check that

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1 statement.

2 And then there was, I think,
3 importantly, the Lin 2011 paper is also relevant.

4 Q Well, as it relates to the Merritt
5 paper, this cite is wrong; right?

6 A I need a moment to --

7 Q Let's look at what Merritt actually
8 found about pelvic inflammatory disease.

9 If you look --

10 MS. O'DELL:

11 If you need a moment --

12 Excuse me. I'm sorry. I didn't mean
13 to interrupt you.

14 If you need a moment to refresh
15 yourself, Dr. Levy, please do.

16 MS. BROWN:

17 Q Sure. And if you -- when you're ready,
18 Doctor, I'll direct you to the second column on
19 page 174, and I want to talk about the last
20 paragraph there that begins "if inflammation."

21 A Page?

22 Q And I'll read it into the record while
23 you orient yourself. It's page 174, right-hand
24 column. Final paragraph states, "If inflammation

1 plays a role in the etiology of ovarian cancer,
2 then it would be expected that PID would be
3 associated with increased risks of ovarian
4 cancer. PID is not associated with elevated risk
5 of ovarian tumors in our data, confirming several
6 previous reports of no association with PID in
7 studies of all subtypes of ovarian cancer."

8 Did I read that correctly?

9 A You did.

10 Q All right. So you cited this study for
11 the proposition that studies have found a
12 relationship between PID and ovarian cancer risk.
13 Right?

14 A No. I said -- I cited -- I said
15 studies have found a relationship, yes, between
16 PID and ovarian cancer risk.

17 Q And, in fact, this study did not find a
18 relationship between PID and ovarian cancer risk.
19 Right?

20 A I think this study found a -- I'm just
21 looking at the...

22 So -- I'm sorry. Would you ask your
23 question again? This -- this study did not
24 find your --

1 Yes, I --

2 Q Sure. I just -- you cited this study
3 for the proposition that it showed there was a
4 relationship between pelvic inflammatory disease
5 and ovarian cancer risk, but, in fact, the study
6 showed the opposite. Correct?

7 A Well, to be clear on the wording,
8 stated that the studies have found a
9 relationship. I didn't indicate whether it was
10 positive or negative.

11 But I think, importantly, the study
12 also has an important paragraph that is probably
13 more related to its inclusion, which is on the
14 same page we were just on, 174, second full
15 paragraph in the discussion.

16 Q One of the things on this page,
17 Doctor --

18 MS. O'DELL:

19 Are you finished, Doctor?

20 A I think important to at least finish
21 that thought.

22 That paragraph reads, "Focusing on talc
23 use, we found that any use of perineal talc was
24 associated with a small but significantly

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1 increased risk of ovarian cancer overall and
2 specifically amongst the invasive and LNP serous
3 tumors, although no clear dose response with
4 increase in duration of use was identified. This
5 finding is consistent with results of previous
6 studies."

7 So in the case of the report and the
8 biologically plausible mechanism that's been
9 supported by these studies, these studies
10 differentiating the process of pelvic
11 inflammatory disease doesn't ex- -- doesn't
12 exclude or refute the inflammatory role or the
13 role inflammation may play in ovarian cancer.

14 Q What this study concludes is that, on
15 balance, chronic inflammation does not play a
16 major role in the development of ovarian cancer.
17 Do you recall reviewing this in connection with
18 your opinions in this case?

19 MS. O'DELL:

20 Object to the form. Misstates the
21 exhibit.

22 MS. BROWN:

23 Counsel, I'll direct you to the last
24 paragraph of the abstract on page 1 which reads,

1 quote, "We conclude that, on balance, chronic
2 inflammation does not play a major role in the
3 development of ovarian cancer."

4 Q Do you see that, Doctor?

5 A I see that.

6 Q And what this study did was it
7 endeavored to look into factors potentially
8 associated with ovarian inflammation to see if it
9 could support the theory that chronic
10 inflammation plays a role in ovarian cancer;
11 right?

12 MS. O'DELL:

13 Object to the form.

14 A I would need to -- this one limitation
15 of this particular paper is that it is connecting
16 inflammation as evidenced by pelvic inflammatory
17 disease and assuming that that source and type of
18 inflammation would be -- the fact that there's
19 not a direct association between -- or an
20 increased risk of ovarian cancer in the presence
21 of pelvic inflammatory disease; therefore,
22 inflammation must not play a role in ovarian
23 cancer. So that is their conclusions.

24 MS. BROWN:

1 Q Well, they looked at a bunch of
2 different inflammatory conditions, didn't they?
3 That was the focus of the study. The authors
4 endeavored to look at a number of different
5 pro-inflammatory factors and see if they
6 influenced ovarian cancer. Do you recall
7 reviewing that?

8 A I do. I think -- but, more
9 importantly, when we look at the -- their
10 specific statements that are surrounding the
11 mechanism we're discussing today, which has to do
12 with talc exposure and perineal talc use, I think
13 their -- their statements in that sense, which
14 have already been read, quite stand on their own.

15 So what this may indicate is a variety
16 of types of inflammation do -- as present in
17 other diseases, those individually do not or may
18 not have a specific role in the progression of
19 ovarian cancer.

20 But it does not -- again, it does not
21 mean that ovarian inflammation at the site of
22 talc exposure in the ovary can't have a role in
23 the progression of disease where -- again, as we
24 were discussing earlier, with inflammation, we're

1 now connecting independent biological processes.

2 And I think you're -- I want to be sure
3 we're clear and not drawing the use of the word
4 "chronic inflammation" as meaning any
5 inflammation and, therefore, if it's not
6 associated with ovarian cancer, that inflammation
7 can't have a role.

8 What we're speaking about in terms of
9 this mechanism is inflammation caused by the
10 perineal use of talcum powder in the ovary and
11 the -- and the -- to explain that increased risk
12 of ovarian cancer, what is a plausible mechanism.

13 Q The authors write, on page 74 -- 174,
14 Doctor, second column, paragraph that begins with
15 "It has been hypothesized," "It has been
16 hypothesized that talc is linked to ovarian
17 cancer development through inflammation," comma,
18 "however evidence linking an inflammatory
19 response with talc contamination of the ovaries
20 is lacking."

21 Do you see that?

22 A I do.

23 Q And you disagree with that statement?

24 A I would -- I would suggest that a

1 number of studies in the literature since the
2 publication of this paper would -- would suggest
3 that these conclusions may have been premature.

4 Q Do you think that, at the time this
5 paper was published in 2008, that Merritt was
6 accurately representing the data as it related to
7 whether chronic inflammation could play a role in
8 the development of ovarian cancer?

9 MS. O'DELL:

10 Object to the form.

11 A I would say that Merritt has an
12 unresolved -- has a number of unresolved
13 conclusions or partial conclusions in their
14 paper, again, including the paragraph we've
15 discussed where they comment on the talc use with
16 an increased risk of ovarian cancer.

17 MS. BROWN:

18 Q Did you see the confidence interval on
19 that finding, Doctor?

20 A I'd have to -- in --

21 Is this in this paper or in the number
22 of the --

23 Q You reference the finding of an
24 association between talc use and ovarian cancer a

1 couple times, and that's a 1.17 relative risk
2 that you're referring to. Is that right?

3 A Where is that?

4 Q I'm looking at -- in the abstract.

5 A Yes.

6 Q Right. And the confidence interval is
7 1.01 to 1.36. Right?

8 A Correct.

9 MS. O'DELL:

10 As to what finding?

11 MS. BROWN:

12 The one we're discussing.

13 Q And, Doctor, you know that one -- a
14 confidence interval that begins with one is not
15 statistically significant?

16 MS. O'DELL:

17 Object to the form.

18 MS. BROWN:

19 Q Did you know that?

20 MS. O'DELL:

21 Object to the form.

22 A Well, I would say the authors have
23 stated in that abstract that it is statistically
24 significant.

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1 MS. BROWN:

2 Q Sure, because it's 1.01. My question
3 to you was do you know that a confidence interval
4 that begins with one is not statistically
5 significant?

6 This finding, Doctor, is barely
7 statistically significant, isn't it?

8 MS. O'DELL:

9 Object to the form.

10 A Again -- again, it's a -- whether it's
11 barely or whether it's tremendously statistically
12 significant, it -- it's still a finding that I
13 would say is in support of -- has been supported
14 by other studies with similar relative risk
15 numbers in the -- in the 1.2 range and above, as
16 indicated.

17 MS. BROWN:

18 Q Finally, Doctor, at the very -- the
19 very last sentence of this Merritt study we're
20 discussing, on page 175, concludes, "However,
21 experimental evidence that perineal talc use
22 elicits an inflammatory response in the ovaries
23 is lacking, and overall we conclude that chronic
24 inflammation does not play a major role in the

1 development of ovarian cancer."

2 And my question for you is what
3 methodology did you employ to consider the
4 findings of the Merritt paper in coming to your
5 opinions contained in your report?

6 MS. O'DELL:

7 Object to the form.

8 A Again, as we've discussed earlier here
9 today, the -- there's been no singular paper that
10 had a specific role in -- in developing the
11 biologically plausible mechanism contained in the
12 report. And, so, this -- this paper, among many
13 others, was -- was used.

14 MS. BROWN:

15 Q Right. But the findings of this paper
16 is that talcum powder doesn't produce an
17 inflammatory response that leads to cancer.

18 Right?

19 A The -- the findings of this paper was
20 that there's not an association of pelvic
21 inflammatory disease and risk of ovar- -- of
22 epithelial ovarian cancer.

23 Q They conclude that chronic inflammation
24 doesn't play a role in the development of ovarian

1 cancer; right?

2 A I think they've -- they've extended
3 that observation regarding pelvic inflammatory
4 disease to that conclusion.

5 But I think the studies that have come
6 after this and other -- certainly other areas of
7 review would suggest that those specific -- the
8 wording of those specific statements may not be
9 the most appropriate representation of the -- of
10 the observations made in the -- in the Merritt
11 paper.

12 Q So did you weight the Merritt paper
13 less than some other papers that came after it?
14 Or how did you --

15 What I'm trying to understand is your
16 methodology for considering this paper, which
17 seems to squarely conclude talc doesn't cause
18 inflammation.

19 MS. O'DELL:

20 Object to the form.

21 A I'm not -- so I would -- I would
22 disagree that -- this paper does not make those
23 conclusions that talc does not cause
24 inflammation. What they --

1 Again, the observations in this paper
2 are regarding chronic inflammation and its -- and
3 its major role in the development of ovarian
4 cancer; and, again, in this -- in the specific
5 individuals that they've looked at, it's in
6 regards to pelvic inflammatory disease.

7 And, so, as far as weighting that
8 paper, it would be similar to other papers and
9 other observations in the sense that it was --
10 that the mechanism that is supported by a wide
11 variety of work considers a history of -- history
12 of work in the talc, inflammation, and ovarian
13 cancer fields both in basic research and
14 epidemiology to come up -- to come to the
15 conclusions and mechanisms that are proposed.

16 I don't -- I can't give you a specific
17 weighting algorithm that was used on any -- any
18 given paper.

19 MS. BROWN:

20 Q Did you consider Merritt's finding that
21 evidence linking an inflammatory response with
22 talc of the ovaries is lacking?

23 A I certainly considered their -- I
24 considered their statements in the -- in the

1 paper. And I would question the dichotomy of
2 the -- of some of their statements regarding talc
3 risk to cancer.

4 And the first question that would come
5 to mind for this particular study is how they
6 assessed talc-related inflammation in --
7 specifically in the ovary. I don't recall seeing
8 how they made that assessment.

9 It, instead, seemed to me that their
10 assessments were based on chronic inflammation as
11 it related to other biological conditions and
12 then extrapolating that to rate of ovarian
13 cancer.

14 Q How do you think one should measure
15 talc-related inflammation in the ovary?

16 MS. O'DELL:

17 Object to the form.

18 A Again, I wasn't asked to -- to provide
19 that opinion. But I would reference the more
20 recent Saed paper which -- and other molecular --
21 and other molecular studies and certainly defer
22 to Dr. Saed as an expert witness to discuss
23 appropriate measurements for talc-related
24 inflammation in the -- in the ovary or ovarian

1 cells.

2 MS. BROWN:

3 Q Have you spoken with Dr. Saed?

4 A I have not.

5 Q Have you requested any information from

6 Dr. Saed?

7 A No, I have not.

8 Q Have you -- would you hold to the same

9 opinion if you did not consider the work of

10 Dr. Saed?

11 MS. O'DELL:

12 Objection to form. Vague.

13 A I -- the work of Dr. Saed is -- is a

14 consideration among the wide variety of other

15 literature contained in here. And Dr. Saed's

16 work for in vitro analysis and the quantitation

17 of specific reactive oxygen species is -- is a

18 factor in and it is in support of the mechanism

19 that I've proposed, which is that that mechanism

20 does not rely on that study or any singular study

21 for it to be valid.

22 MS. BROWN:

23 Q The mechanism you proposed, Doctor, is

24 not yet generally accepted in the scientific

1 community. Would you agree?

2 MS. O'DELL:

3 Object to the form.

4 A I wouldn't have a basis for that
5 opinion. As -- as we talked about earlier, I
6 haven't shared this mechanism to ask for that
7 opinion.

8 MS. BROWN:

9 Q You haven't published the proposed
10 mechanism that is the subject of your report. Is
11 that right?

12 A That's right.

13 Q You haven't discussed the proposed
14 mechanism that is the subject of your report with
15 any of your colleagues at HudsonAlpha; correct?

16 A That's correct.

17 Q So whether or not the proposed
18 mechanism that is the subject of your report
19 would be accepted by your peers in the scientific
20 community, that's not something you have yet
21 evaluated; correct?

22 MS. O'DELL:

23 Object to the form.

24 A My -- I wasn't requested to provide a

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1 biologically plausible mechanism that was also
2 peer-reviewed, and I would rely on or point you
3 to a number of other expert reports, particularly
4 in the epidemiology space from this case, where
5 you'll find a great many parallels to -- to this
6 case.

7 So I, instead, would state
8 independently myself and other respected
9 scientists have essentially developed the same
10 opinions regarding mechanism in this -- in this
11 particular space.

12 MS. BROWN:

13 Q Is there another plaintiffs' expert
14 that you're aware of who holds the same opinion
15 as you do on biological plausibility?

16 A Yes.

17 Q Who's that?

18 A Patricia Moorman, who is an
19 epidemiologist whose report I had the opportunity
20 to read yesterday.

21 Q Is there -- and -- and even though
22 she's an epidemiologist, Dr. Moorman has a view
23 on biological plausibility? Is that right?

24 MS. O'DELL:

1 Object to the form.

2 A She has a view on --

3 In her report was a -- a view on
4 mechanism -- on mechanism, which included the
5 discussion of inflammatory response and its role
6 in ovarian cancer, which parallels this report.

7 MS. BROWN:

8 Q Do you consider your proposed mechanism
9 that is the subject of your report to be a novel
10 concept in the scientific world?

11 MS. O'DELL:

12 Object to the form.

13 A Which part?

14 MS. BROWN:

15 Q Any part.

16 MS. O'DELL:

17 Object to the form.

18 A Again, I -- my -- the -- what was
19 requested of me was not to develop a novel
20 concept or even to describe an untested
21 hypothesis. What was requested of me was to
22 review the available literature and provide a
23 biologically plausible mechanism for talc
24 exposure to ovarian cancer. And, so, that's

1 what -- that's what my report provides.

2 MS. BROWN:

3 Q Do you think there could be other
4 biologically plausible mechanisms by which talcum
5 powder would be associated with ovarian cancer?

6 A I haven't been asked to -- to make a
7 review related to other biological mechanisms. I
8 was asked to develop a biologically plausible
9 mechanism. And upon review of the totality of
10 the literature, this mechanism that -- that I've
11 presented and provided in the report is, in my
12 opinion, the correct mechanism.

13 Q Did you have complete autonomy in your
14 task to develop a biologically plausible
15 mechanism?

16 A Yes.

17 Q Were there any limitations on how you
18 should go about developing this biologically
19 plausible limita- -- mechanism?

20 MS. O'DELL:

21 Object to the form of the question to
22 the degree that the question seeks --

23 MS. BROWN:

24 Form.

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1 MS. O'DELL:

2 No, no. If it goes to conversations
3 with counsel, it is not form. It is
4 attorney-client privilege and it's protected.
5 Work product privilege is protected.

6 And, so, Dr. Levy --

7 MS. BROWN:

8 No. Counsel --

9 MS. O'DELL:

10 Excuse me. Excuse me. I'm directing
11 my witness based on privilege, and I can do that.

12 To the degree that counsel is trying to
13 seek the substance of discussions you had with
14 counsel, those are protected, and I direct you
15 not to answer.

16 To the degree there's something in your
17 mind to respond that's not that, you may -- you
18 may respond.

19 MS. BROWN:

20 Q And as -- as counsel well knows,
21 because we've had this discussion earlier this
22 week, the federal rules allow discovery of any
23 material you relied on in forming your opinions.

24 And, so, my answer here -- my question

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1 for you here, Doctor, is, were -- was there any
2 limitation placed on you that you relied on in
3 trying to develop your biologically plausible
4 mechanism?

5 MS. O'DELL:

6 What's allowed -- you're well aware of
7 this, counsel, I know -- that what's discoverable
8 is are there materials considered -- you can ask
9 him that -- was there assumptions that he was
10 asked to make -- that's discoverable -- and the
11 compensation. Those are the three things. Not
12 conversations between counsel and Dr. Levy.

13 So --

14 MS. BROWN:

15 Counsel, you can instruct or we'll get
16 the judge. We do not have time for your
17 speeches. We're trying to finish up and let
18 other people -- other people ask questions.

19 MS. O'DELL:

20 That's straight from the rules. You're
21 well aware of that.

22 MS. BROWN:

23 So here's the question. If you want to
24 instruct, we'll take a break and get the judge.

1 Q Did you rely on any instruction from
2 counsel regarding any limitations on how you were
3 to attempt to develop your biologically plausible
4 mechanism?

5 A No. I was -- I was not provided --
6 there were no --

7 I'm trying to make sure I answer to be
8 correct. But my very simple and direct answer is
9 the requests for the report were very succinct
10 and were given without limitation.

11 Q Did you try to develop any mechanism
12 that you rejected in connection with your report?
13 MS. O'DELL:

14 Object to the form. Vague.

15 A So I would best answer that by saying I
16 did not develop an initial mechanism and,
17 instead, began a literature review looking at the
18 available literature in talcum powder
19 inflammation in cancer, ovarian cancer, and then
20 in related subjects, and then, through the course
21 of that review, was able to synthesize the
22 opinion that you have, that we've been
23 discussing, in the report.

24 MS. BROWN:

1 Q Do you consider the biologically
2 plausible mechanism that is the subject of your
3 report to be a hypothesis?

4 MS. O'DELL:

5 Object to the form. Asked and
6 answered.

7 A No, no. In fact, it is not. And
8 it's -- I think it's very fundamentally different
9 than a hypothesis.

10 Because, again, to state, the
11 activities that were undertaken was a review of
12 the literature and then, based on that review, a
13 mechanism that was biologically plausible. It is
14 not hypothetical.

15 MS. BROWN:

16 Q Have you tested your biologically
17 plausible mechanism?

18 MS. O'DELL:

19 Object to the form.

20 A Tested in the sense of --

21 So I would -- I would answer that as --
22 in -- in my opinion, I would suggest that this
23 has been tested based on following the completion
24 of the report and reading other similarly derived

1 or similarly requested both literature, some of
2 the publications that we've been discussing, as
3 well as other expert reports that have, as we've
4 just discussed, some parallel aspects.

5 So, from a formal scientific process,
6 that is -- would not, I think, be considered a
7 formal test. But from the perspective of this
8 biologically plausible mechanism, other
9 scientists undertaking similar methodology came
10 up with similar results.

11 And, so, therefore, I would say that
12 this report is -- continues to be supported by
13 independent reviews and content.

14 MS. BROWN:

15 Q The other scientists that you just
16 referenced are also paid experts for the
17 plaintiffs; is that right?

18 MS. O'DELL:

19 Object to the form.

20 A I don't have knowledge of that
21 specifically.

22 MS. BROWN:

23 Q Well, when you said other experts
24 looking at the same thing came up with a similar

1 mechanism, you mean other experts in this
2 litigation?

3 MS. O'DELL:

4 Object to the form. Misstates his
5 testimony.

6 A Other -- other material -- the
7 materials that I was -- that I was provided.

8 MS. BROWN:

9 Q And those materials are in the form of
10 other expert reports like yours; right?

11 MS. O'DELL:

12 Object to the form.

13 A They are.

14 MS. BROWN:

15 Q Are you aware of any nonlitigation
16 expert that has arrived at the same biologically
17 plausible proposed mechanism as you?

18 MS. O'DELL:

19 Object to the form.

20 A Well, I think -- yeah, in the sense --
21 in the sense of the number of publications we've
22 been discussing and some of the more recent both
23 reviews and -- and Saed's paper, I suppose, as
24 we've been discussing, Dr. Saed has been funded

1 for some of this work, but I would counter that
2 with sponsorship of -- of studies that are
3 subsequently peer-reviewed, I think are generally
4 held to a scientific standard and rigor, and
5 would suggest that his most recent work would
6 fall under that and -- and, therefore, I would
7 not consider that in the same realm as an expert
8 report.

9 MS. BROWN:

10 Q Are you aware that the plaintiffs'
11 lawyers funded Dr. Saed's studies?

12 A I am.

13 Q How do you know that?

14 MS. O'DELL:

15 Don't speculate. If you know it,
16 testify to it.

17 A No. I'm thinking of --

18 That was disclosed during the
19 discussion of the -- of the paper, and the
20 question I asked and actually looked on the paper
21 was to --

22 And this -- this was getting to my own
23 opinion as to the appropriateness and the
24 potential scientific rigor of the paper, and that

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1 was whether or not Dr. Saed disclosed that
2 relationship, which is, of course, ethically a
3 requirement for sponsored research. And, indeed,
4 that sponsorship is made in the paper.

5 MS. BROWN:

6 Q Was it important to you --

7 Did you ask Dr. Saed about the funding
8 for his paper?

9 A I did not. As we -- as we discussed, I
10 haven't spoken with him.

11 Q Were you troubled by the fact that
12 Dr. Saed's disclosure does not reference which
13 side of the litigation he's working for?

14 MS. O'DELL:

15 Object to the form.

16 A Are you asking for my opinion on if it
17 troubled me?

18 MS. BROWN:

19 Q Yeah.

20 A No.

21 Q It sounds like you did a little
22 investigation and you were satisfied with the
23 disclosure. Was that your testimony?

24 MS. O'DELL:

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1 Object to the form. He didn't use the
2 word "investigation."

3 A I was satisfied seeing a disclosure
4 made regarding funding, which, again, in the
5 scientific climate I would -- or I would state
6 simply I viewed the support of that study which
7 subsequently goes out to peer review functionally
8 equivalent to pharmaceutical support of a study
9 involving a drug or a condition or a treatment.

10 The reality of the scientific space
11 is -- is -- is funding sponsorship comes from a
12 variety of cases. And in each institution,
13 HudsonAlpha certainly, I'm positive Wayne State
14 has a conflict of interest review board which
15 Dr. Saed has to report to as far as the -- how he
16 manages that potential conflict of interest. And
17 given that he's at a reputable institution that
18 I've actually done a fair amount of review work
19 with over the years, being Wayne State, I'm
20 reasonably -- or I would say I'm quite confident
21 that his conflict of interest has been managed
22 appropriately for the -- for the study that was
23 reviewed.

24 MS. BROWN:

1 Q Why is it important, in your mind, to
2 disclose funding for a study?

3 A Well, it's, you know, ethical premise
4 of -- of most scientific research or really all
5 extramurally funded research that the funding
6 sources are -- are always disclosed. And that's
7 true for publication as well as presentation.

8 And, so, I think most -- most
9 scientists, during presentation, will present a
10 slide that shows their -- their funding support
11 and all of its sources regard- -- whether it's
12 public or private.

13 And then you'll notice in vast majority
14 of publications, if they are grant supported,
15 again, whether that grant is from a public or a
16 private institution, those things are referenced.
17 And, in fact, the U. S. Government has a
18 requirement that grants be referenced in their --
19 in any publications that were supported by that
20 money.

21 Q Do you have any critiques of either of
22 Saed's papers?

23 A No. Not at this time.

24 Q Do you have any questions or anything

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1 that doesn't make sense to you, having reviewed
2 the most recent one or the 2017 one?

3 A No. My focus, particularly on the most
4 recent one, I actually found his molecular
5 studies to be quite comprehensive and --

6 So there was -- there was no specific
7 concerns that -- that I was able to identify.

8 And, again, the -- in the -- in the version of
9 the paper that -- that I -- that I was given.

10 Q And did you have any opportunity to
11 check to see if you had an earlier version of
12 that paper?

13 A Oh, I -- I'll be sure and do that at
14 the next break.

15 Q Okay. Why don't we go ahead and take a
16 break now. You'll take a look, if you wouldn't
17 mind, to see if you have something other than
18 what we've marked at the deposition.

19 I'm going to renew -- review my notes.
20 I'm close to finishing, and then I'll hand it
21 over to my colleague, Mr. Ferguson, who I think
22 will have some questions for you as well. Okay,
23 Doctor?

24 A Uh-huh.

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1 Q Thank you, Doctor.

2 VIDEOGRAPHER:

3 Going off the record. The time is 3:33

4 p.m.

5 (OFF THE RECORD.)

6 VIDEOGRAPHER:

7 We're back on the record. The time is

8 3:48 p.m.

9 MS. BROWN:

10 Q Welcome back, Doctor.

11 Did you have an opportunity to take a
12 look if you had an earlier version of Dr. Saed's
13 manuscript?

14 A I did.

15 I did not.

16 Q Okay. And, so, during this deposition,
17 you've referred from time to time to Dr. Saed's
18 2018 paper. Is that right?

19 A (Nods affirmatively.)

20 MS. O'DELL:

21 Object to the form. Excuse me.

22 MS. BROWN:

23 Q And you received that paper after you
24 authored your report in this case; right?

1 MS. O'DELL:

2 Object to the form.

3 A So I was referring --

4 Yes. I -- I -- the manuscript we were
5 discussing was received after the completion of
6 this. But, as we discussed earlier, the
7 materials in the paper were presented in abstract
8 form or long abstract form, and those are
9 referenced in the report.

10 MS. BROWN:

11 Q And just to close the loop on one thing
12 before I hand it over to my colleague,
13 Mr. Ferguson, you had referenced an animal study
14 by Woodruff earlier in the day. Do you remember
15 that?

16 A Yes.

17 Q That paper doesn't have anything to do
18 with talc; right?

19 MS. O'DELL:

20 Object to the form.

21 A Let me --

22 Yes, I -- you're -- the Woodruff 1979
23 paper is not the one I was -- I was wrong on the
24 author. Give me a moment to...

1 MS. BROWN:

2 Q And if that's not the one you were
3 thinking of, Doctor, we can move on.

4 A I was thinking Henderson 1971.

5 Q And that's not an animal study; right?

6 A Maybe this -- this isn't the same one,
7 then. I can certainly find it at the end if --

8 The -- it was a 1971 study involving a
9 rat model that the major point and conclusion of
10 the study was perhaps something that we've
11 discussed that's been now well accepted that the
12 talc can migrate, after exposure, into the
13 ovarian tissue.

14 Q Are you aware of any study, Doctor,
15 that talc on the exterior of a woman's vagina can
16 migrate up the fallopian tubes to the ovary?

17 MS. O'DELL:

18 Object to the form.

19 A I am not aware of a study that tested
20 that specifically.

21 MS. BROWN:

22 Q And did you consider, in connection
23 with your opinions here, IARC's finding that the
24 science regarding migration is, quote, "weak"?

1 MS. O'DELL:

2 Object to the form.

3 A My -- my primary consideration of IARC
4 was their classification of the talc and the --
5 and the fibrous talc, and I don't recall their
6 conclusions of the migration science being weak.

7 And, in fact, it appears, as stated by
8 the FDA, that the -- the migration question is --
9 is well resolved.

10 MS. BROWN:

11 Q Finally, Doctor, in connection with
12 your opinions in this case, did you consider
13 articles regarding whether stick lesions evidence
14 inflammation?

15 A I'd have to review some of the
16 literature for stick lesions specifically. But
17 that --

18 Can you -- what are you referring to by
19 stick lesions?

20 Q So do you understand that it's now
21 believed, in terms of the -- where ovarian cancer
22 begins, that it begins in the fallopian tubes,
23 epithelial ovarian cancer?

24 A I certainly would agree that a -- the

1 site of initiation, whether -- that it can begin
2 in the fallopian tubes, yes, that there's been
3 studies that have shown that evidence.

4 Q And some of the early lesions that have
5 been found in the fallopian tubes are sometimes
6 referred to as stick lesions. Are you familiar
7 with that?

8 MS. O'DELL:

9 Object to the form.

10 A I'm not.

11 MS. BROWN:

12 So you haven't looked at any studies
13 that have looked at stick lesions that have been
14 removed from women to see if there was any
15 evidence of inflammation?

16 MS. O'DELL:

17 Object to the form.

18 A That -- that -- I don't recall that as
19 part of the review.

20 MS. BROWN:

21 Q Fair enough.

22 No further questions. I'll hand it
23 over to Mr. Ferguson.

24 MR. FERGUSON:

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1 Thank you.

2 EXAMINATION

3 BY MR. FERGUSON:

4 Q Good afternoon, Dr. Levy. My -- my
5 name is Ken Ferguson, and I represent Imerys in
6 this matter. Do you know who Imerys is?

7 A Only that they're a mining company.

8 Q Okay. And I have some questions for
9 you. I apologize for my voice. I've kind of had
10 my allergies and then going into a cold, so it's
11 kind of -- kind of stuffy. So I apologize.

12 If you have trouble hearing me or
13 understanding me, let me know. Okay?

14 A Okay.

15 Q And -- and just -- I know you've been
16 at this with Miss Brown for a little while, but
17 if there's any question that you don't understand
18 that I'm asking you, just let me know, and I'll
19 restate it so I can make sure that we're
20 communicating. Okay?

21 A Okay.

22 Q I want to talk to you, first of all,
23 about a little bit more about what you do at
24 HudsonAlpha Institute. So in the what's called

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1 the Genomic Services Laboratory --

2 Right? There's one of those at

3 HudsonAlpha; right?

4 A There is.

5 Q Do you perform services there such as

6 running clinical samples to report results to

7 healthcare providers? Is that the kind of things

8 you do?

9 A To be -- to be clear and to,

10 importantly, differentiate the regulated lab

11 versus the research laboratory, the Genomic

12 Services Laboratory is a -- is a entity of

13 HudsonAlpha that is responsible for research

14 activities.

15 There is a separate wholly owned

16 subsidiary of HudsonAlpha creatively named the

17 Clinical Services Laboratory. So that laboratory

18 is the laboratory that performs the testing. And

19 to hopefully not provide a level of confusion,

20 but the two laboratories coexist in the same

21 space. And what this means is I have staff and

22 equipment. Some is dedicated to clinical, some

23 is dedicated to research, and some are shared

24 between the two.

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1 So, in summary, the best way to
2 consider the laboratory is that it's a clinical
3 regulated laboratory that also performs research.

4 Any projects under that research
5 umbrella are referred to as being in the Genomic
6 Services Laboratory. Anything clinical is
7 referred to the Clinical Services Laboratory.
8 That lab has been CLIA-licensed now for going on
9 five -- just past four years and has been
10 CAP-accredited for three and a half.

11 Q So is it the Clinical Services
12 Laboratory, then, that would perform services
13 like running clinical samples to get results to
14 healthcare providers?

15 A That's correct.

16 Q And -- and among those things that the
17 Clinical Services Laboratory does, is that
18 restricted to whole genome sequencing?

19 A Our currently -- the only publicly
20 disclosed and validated test for the Clinical
21 Services Laboratory is whole genome sequencing.

22 We have two other laboratory-developed
23 tests, or commonly referred to as LDTs, that are
24 run in a -- as a private assay for some clinical

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1 trials, so they're not publicly available and to
2 date have not been publicly disclosed. They're
3 protected under confidentiality agreement.

4 And the Clinical Services Laboratory
5 this year will launch a number of other tests
6 that we have publicly disclosed. Those include
7 whole exome sequencing, an oncology panel known
8 as the TruSight Tumor 170, which profiles 170
9 genes with -- that have been -- that have known
10 involvement in cancer risk and progression, and
11 as well as a 500 panel of similar form.

12 Q So let me talk to you a little bit
13 about your prior position. You were at
14 Vanderbilt University Medical Center; correct?

15 A Correct.

16 Q And you were an assistant professor?
17 Is that correct?

18 A The titles I held there was research
19 assistant professor and then assistant professor,
20 and then I was a associate professor as an
21 adjunct faculty for a number of years after
22 joining HudsonAlpha. So I had to progress
23 through a few of the academic ranks at
24 Vanderbilt, but all of them in the professor

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1 realm.

2 Q As an assistant professor, were you
3 appointed on a tenure track?

4 A Yes.

5 Q And do you know generally how many
6 years after appointment as an assistant professor
7 is a tenure decision at Vanderbilt typically made
8 in that department?

9 A It varies from probably five to nine.

10 Q Did you ever achieve tenure at
11 Vanderbilt?

12 A Actually, I was up for tenure the year
13 that I moved to HudsonAlpha.

14 Q So --

15 A So, technically, I, which will sound
16 odd, I was promoted to associate professor upon
17 leaving.

18 Q Okay.

19 A In an adjunct role.

20 Q So were you turned down for tenure
21 or --

22 A I was not. I never -- I -- the
23 opportunity at HudsonAlpha predated the time that
24 I would have gone up for tenure. I had a number

1 of pre-reviews for tenure. There were no
2 concerns with that progress. But, based on both
3 funding as well as publication records, I wasn't
4 overly concerned with that.

5 But the opportunity to be able to do --
6 and the scale of operations at HudsonAlpha was --
7 was too good to turn down, as far as remaining at
8 Vanderbilt.

9 Q So you were neither granted tenure nor
10 denied tenure. Is that fair to say?

11 A That's fair to say.

12 I think the best evidence for the
13 relationship at Vanderbilt after my leaving was I
14 continued as an adjunct faculty in the same
15 department, again with change in title, for a
16 number of years after joining HudsonAlpha. So it
17 was a -- certainly, I wouldn't characterize it as
18 a negative departure from the institution. And I
19 still remain a collaborator with a number of
20 colleagues there.

21 Q Do you have a copy of your report in
22 front of you?

23 A I do.

24 Q Okay. What I'm gonna do is I'm gonna

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1 try to go through, probably in -- in order,
2 portions of your report that I want to ask about
3 and try to make sure I don't cover things that
4 Miss Brown's already covered.

5 Can you look at page 5 of your report?

6 A Yes.

7 Q So there -- and I'm looking at number 2
8 on page 5, Acquired Somatic Gene Mutation.

9 Do you see that?

10 A I do.

11 Q And you say there that --

12 I'm skipping the sentences. If you
13 need to go back, feel free.

14 -- "Biological and lifestyle exposures,
15 such as viruses, obesity, hormones and chronic
16 inflammation, are also known to result in
17 cancer-causing mutations."

18 Right?

19 A I see that sentence.

20 Q Okay. Wouldn't you agree that the
21 association between obesity and cancer risk is
22 just that, an association and not a known
23 cause-and-effect relationship?

24 MS. O'DELL:

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1 Object to the form.

2 A I would state that it is known that
3 cancer rates increase in a number of unhealthy
4 conditions, including obesity. But I am not
5 aware of a -- of any studies that have
6 illustrated a causal effect directly between
7 obesity and cancer.

8 MR. FERGUSON:

9 Q And, specifically, isn't it true that
10 there is no direct in vivo experimental evidence
11 that obesity causes cancer-causing mutations?

12 A I would have to review the literature
13 to -- before answering that question. But the
14 relationship between obesity and cancer risk
15 is -- is quite well established. And I think for
16 us to discuss that in more detail, we'd have to
17 start delving into some of the specifics around
18 the physiological changes related to obesity and
19 whether those specific physiological changes play
20 a role in cancer.

21 Q And, just below that, the last sentence
22 in that paragraph, you say, "These mechanisms may
23 be direct, such as radiation directly damaging
24 DNA, as well as indirect, such as an external

1 agent causing a cellular -- cellular reaction or
2 inflammatory response that then leads to DNA
3 damage or mutation."

4 What cellular reactions are you
5 referring to that result in DNA damage or
6 mutation?

7 A So the presence of reactive -- so a few
8 different things. Primarily, along the
9 discussions for today, the presence of reactive
10 oxygen species which can directly -- which are a
11 cellular reaction that can then cause -- directly
12 cause DNA damage.

13 There's protein oxidation effects that
14 are similar to that, in the sense that you have a
15 chemical change and a cellular component that
16 results in a -- in a protein activity change,
17 again leading to potential DNA damage.

18 And then you can have --

19 So those are two -- two examples of
20 cellular reactions to that.

21 Q And -- and maybe you just explained it,
22 but I wanted to make sure I'm clear. What is the
23 mechanism by which an inflammatory response
24 results in DNA damage?

1 A It varies. So the -- the --
2 "inflammatory response" is a bit general. So
3 depending on specific type of cellular
4 recruitment and cellular damage through the
5 release of cytokines, the release of oxidative
6 damaging materials from cells like granulocytes,
7 you know, or the -- even the cell's own
8 production of reaction to -- reactive oxygen
9 species, such as from the mitochondria, which is
10 the most common sync -- or most common source of
11 reactive oxygen species in the cell.

12 And, so, those are some examples of --
13 of that relationship between an inflammatory
14 response and that cellular reaction.

15 Q Reactive oxygen species are not the
16 same thing as inflammation; correct?

17 A I would say reactive oxygen species are
18 a hallmark of inflammation.

19 Q But they're not the same thing.

20 MS. O'DELL:

21 Object to the form.

22 A The -- well, they are --

23 Again, reactive oxygen species are a
24 component of inflammation. So they're -- the

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1 words are two -- two different definitions, but
2 they are a component.

3 MR. FERGUSON:

4 Q Would you agree that reactive oxygen
5 species are a normal part of cell physiology?

6 A Yes, absolutely.

7 Q And the major source of reactive oxygen
8 species comes from inside the cell and is
9 produced in mitochondria?

10 A A source, and depending on the site of
11 the physiology. So a normal, healthy cell not
12 under stress or injury would be -- then, yes,
13 that's a true statement.

14 Under different physiological
15 conditions, that statement may not be true.

16 Q Can you distinguish reactive oxygen
17 species produced inside a cell from reactive
18 oxygen species produced outside the cell?

19 A What do you mean? So by -- by
20 "distinguish," you mean --

21 Q Can you tell the difference?

22 A I'm just thinking if there's a way to
23 measure.

24 So you can measure the effects of

1 exogenously introduced reactive oxygen species
2 and then compare that to the measurement of
3 endogenously produced reactive oxygen species.

4 But as far as determining the
5 difference if the cellular integrity is not
6 intact, I'm not aware of a method to do that.

7 Q Would you agree that generation of
8 reactive oxygen species is an inevitable
9 consequence of aging in aerobic organisms?

10 MS. O'DELL:

11 Object to the form.

12 A So reactive oxygen species are a --
13 are present at all stages of life. And aging, as
14 a biological phenomenon, is probably one of the
15 most variable phenomenon that exists.

16 And specific to reactive oxygen
17 species, the diet, lifestyle, and genetics of
18 that individual will drastically change that.

19 And a new area of research that my
20 laboratory has been undertaking for a short
21 time --

22 And, so, I don't have specific
23 publications, and it's really not -- I promise
24 it's not taking us too far afield.

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1 -- but is the concept of your annual
2 age versus biological age. And my lab has some
3 assays that are based on epigenetics as well as
4 some metabolomic markers. And what we found --
5 now, in very, again, preliminary data -- that
6 individuals will vary by plus or minus 15 years
7 from physiological age to annual age based on,
8 again, a number of lifestyle factors not
9 important for this study.

10 But the point I'm making is the
11 discussion about level of reactive oxygen species
12 and its association with age is actually quite
13 variable based on the long -- or based on the
14 current physiological activity of that person.

15 Stated very simply, which is probably
16 something we all know, the better shape you're
17 in, the younger your physiology will appear. And
18 you can actually modulate that quite quickly,
19 meaning that a person who's 60 and has made poor
20 lifestyle choices can actually gain back quite a
21 bit of that physiological age quite quickly.

22 And so, again, to directly answer your
23 question, a annual age-related conclusion
24 regarding production of reactive oxygen species

1 would be very difficult.

2 MR. FERGUSON:

3 Q In your report, on this same page, you
4 discuss the fact that, even if someone has a
5 genetic mutation that predisposes them to cancer
6 doesn't mean that he or she is certain to get
7 cancer. Correct?

8 A That is correct.

9 Q So there is a -- a random component to
10 the effects of known cancer-causing agents.
11 Right?

12 MS. O'DELL:

13 Objection to form.

14 A There is a complicated relationship
15 between genetics, environment, and expose -- or
16 environment, including exposure and lifestyle,
17 and the progression of cancer.

18 Perhaps the -- a summary analogy is the
19 more predisposing mutations that an individual
20 has, it's -- it's equivalent to their body is
21 rolling the dice more often to collect a mutation
22 sufficient to cause cancer than somebody who does
23 not have the same genetic background.

24 And there's -- there's many, many lines

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1 of evidence. Probably the most prominent is
2 BRCA1 and 2 mutation and the role it plays in
3 increased risk of breast and ovarian cancer.

4 MR. FERGUSON:

5 Q Wouldn't you agree that even the
6 inherited susceptibility cannot entirely explain
7 this random component of some people getting
8 cancer when exposed and some people not?

9 MS. O'DELL:

10 Objection to form.

11 A DNA -- so that, it's very
12 gene-dependent. So BRCA1 and 2 is the example
13 given. That is correct, that if you have a BRCA1
14 and -- 1 or 2 mutation, you are not guaranteed to
15 get cancer.

16 Corollary to that is if you do not have
17 a BRCA1 and 2 mutation, your relative risk for
18 cancer does not change, meaning that you're at no
19 less of a risk than somebody -- somebody else who
20 doesn't have that mutation.

21 I should state that there are other
22 genes. P53 is a good example that was mentioned
23 earlier. If you carry a mutation in that gene,
24 the probability that you'll get cancer, assuming

1 you don't die from something else, is almost
2 certain, meaning that it's in the mid to high 90
3 percents if you -- if you live until a late age.

4 MR. FERGUSON:

5 Q Further down this paragraph, you
6 indicate that "An inherited gene mutation could
7 instead make one more likely to develop cancer
8 when exposed to certain cancer-causing
9 substances."

10 Correct? That's your statement?

11 A Yes.

12 Q Can you provide any examples in which a
13 woman with an inherited mutation in a particular
14 gene has been demonstrated to have more
15 sensitivity to developing ovarian cancer as a
16 result of exposure to an environmental agent?

17 A Not for ovarian cancer specifically. I
18 would need to review --

19 There is a -- I've seen report of a
20 single gene related to ovarian cancer, which,
21 again, I would have to do a bit of searching to
22 be sure I'm naming the correct gene, but I --
23 where that has a much high- -- increased risk
24 specific to ovarian cancer, but I do not recall

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1 if there was a measurement of any exogenous
2 exposure risk that amplified that effect or not.

3 But I think the -- as a general
4 premise, it is a -- well established in cancer
5 biology that any mu- -- any mutation that results
6 in a burden related to DNA repair, related to
7 cell cycle control, you are more susceptible to
8 cancer.

9 In one of our lines of research where
10 we do have some publications, in pediatric
11 cancer, I would simply point to in approximately
12 50 percent of adults who are survivors of
13 childhood cancer will develop a second cancer
14 event primarily because their -- the fact that
15 they developed a childhood cancer generally means
16 you are predisposed to that condition.

17 And -- and, as evidenced in the
18 observations we've done in the analysis of
19 thousands of patients in collaboration with
20 St. Jude and the children's oncology group, we've
21 identified now a ability to do genetic counseling
22 in those individuals and predict with very high
23 accuracy what their secondary cancer is likely to
24 be.

1 And the point of my mentioning this is
2 to illustrate that an early predisposition to --
3 or a significant predisposition to cancer that
4 results in a early cancer event, those
5 individuals show a lifetime increase in risk of
6 approximately -- they're -- they're approximately
7 six times, depending on the disease, to 13 times
8 more likely to get that -- to get a secondary
9 disease.

10 So there clearly is a relationship to
11 predisposition in -- in oncology -- or in rate of
12 cancer event.

13 Q Okay. And I appreciate your response.
14 But remember that my question was related to
15 ovarian cancer, and -- and we went a little
16 afield from ovarian cancer.

17 And I want to ask you another question
18 in that regard. Can you provide any example in
19 which a woman with an inherited mutation in a
20 particular gene has been demonstrated to have
21 more sensitivity to developing ovarian cancer as
22 a result of exposure to talcum powder?

23 MS. O'DELL:

24 Object to the form.

1 Answer the question.

2 A So the mechanism we proposed would be
3 independent of -- of that predisposition. But I
4 would have the opinion that an individual with
5 any predisposition mutation, regardless of the
6 gene but -- and -- in ovarian cancer, that they
7 would be a more fragile individual as -- when it
8 comes to this exposure under the mechanism that
9 we've been discussing today.

10 MR. FERGUSON:

11 Q Okay. And what I'm looking for is some
12 example or some literature in that regard.

13 A I would -- I would have to -- I would
14 have to look --

15 Q Okay.

16 A -- to see.

17 Q So what you've told me is that's your
18 opinion, but you don't have any references for it
19 as you sit here?

20 MS. O'DELL:

21 Objection to form.

22 A So my -- what was -- I was requested to
23 provide this biologically plausible mechanism,
24 and part of that request was not necessarily

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1 include the influence on that mechanism that
2 specific gene mutations or inherited risks may
3 have within relation to ovarian cancer.

4 So I'd certainly be delighted to pause
5 for a moment and take -- you know, and -- and
6 work on that -- give you that -- see if I can
7 give you that specific example.

8 MR. FERGUSON:

9 Q But you can't as you sit here?

10 A I cannot.

11 Q Okay. So let's look at -- further down
12 on page 5, you have a section entitled "The Role
13 of Genetics in Ovarian Cancer." Correct?

14 A Correct.

15 Q And I want to look at a reference that
16 you -- you have cited. And let me mark this as
17 an exhibit, please. I guess I can mark it.

18 (DEPOSITION EXHIBIT NUMBER 21
19 WAS MARKED FOR IDENTIFICATION.)

20 MR. FERGUSON:

21 Q Exhibit 21 is the Nunes article. Have
22 you seen that?

23 A I have, yes.

24 Q Okay. So if we look at page 5, at top

1 of the page, you indicate that ovarian cancer is
2 the major cause of death from gynecologic disease
3 and the second most common gynecologic malignancy
4 worldwide; correct?

5 A Correct.

6 Q And then in your report you cite Nunes
7 and Serpa, the article we've just marked as
8 Exhibit 21, as well as Siegel and Torre; correct?

9 A Yes.

10 Q If we look at page 2 of the Nunes
11 article, the exact same sentence appears on -- at
12 the bottom of page 2 under the heading of
13 "Ovarian Cancer, an Overview"; correct?

14 A Correct.

15 Q Right.

16 A That's correct.

17 Q Okay. And it's --

18 A It's not quite the same sentence, given
19 that it's the same initial statement, not an
20 identical sentence.

21 Q Very close to identical?

22 A Well, they -- they both -- they both
23 introduce the same facts.

24 Q Okay. Then if we go down a little bit

1 further and you have a sentence that starts
2 "epithelial ovarian cancer." Correct?

3 MS. O'DELL:

4 On page 6 there?

5 MR. FERGUSON:

6 Yeah. I apologize. Yeah, it is.

7 A Yep.

8 MR. FERGUSON:

9 Q It's on page 6. It's the, I believe,
10 the last sentence of the partial paragraph at the
11 top of 6. See it?

12 A I do.

13 Q Okay. And you say, "Epithelial ovarian
14 cancer (EOC) includes most malignant ovarian
15 neoplasms" -- you cite Chan, 2006 -- "that can be
16 classified based on morphologic and molecular
17 genetic features into the following types:
18 Serous" -- and, in parentheses, "(OSC) low and
19 high grade); endometrioid (EC), clear cell,
20 (OCCC), and mucinous (MC) carcinomas."

21 Correct?

22 A Correct.

23 Q Okay. And then if we look back at page
24 2 of Nunes, in the second sentence of the first

1 paragraph under "Ovarian Cancer, an Overview,"
2 the nearly identical sentence appears there.

3 Correct?

4 MS. O'DELL:

5 Object to the form.

6 A The two sentences stating the same
7 fundamental facts regarding ovarian cancer and
8 the histological types are -- yes, I agree.

9 MR. FERGUSON:

10 Q With almost the same wording.

11 MS. O'DELL:

12 Object to the form.

13 A They have similar wording.

14 MR. FERGUSON:

15 Q Remarkably similar; correct?

16 MS. O'DELL:

17 Object to the form.

18 A I wouldn't call it -- so they --

19 Again, we're stating fundamental basic
20 facts around histological type and following a
21 number of, again, factual observations for what
22 the state of the art for genetic knowledge
23 in -- in different genes and different proteins
24 is as it relates to our understanding of -- of

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1 cancer with, again, appropriate reference for
2 those -- for those studies.

3 MR. FERGUSON:

4 Q And then if we look at the following
5 paragraphs, the first full paragraph there on
6 page 6, in your report you have a sentence that
7 starts "low grade OSC cases generally have
8 genetic alterations" in a number of items you've
9 listed; correct?

10 A Correct.

11 Q Okay. And that sentence ends with the
12 words or "p13/Ras/Notch/FOXm1." Correct?

13 A Correct.

14 Q Okay. And then if we go back to Nunes,
15 if you look at that same paragraph we've been
16 talking about -- and those -- there's an
17 introductory phrase that you don't have, and then
18 it starts with "low grade OSC generally
19 comprising." Slightly different wording, but you
20 list the same types of receptors and the same
21 types of items. Correct?

22 A Yes. That's providing a review of,
23 again, the known associations between specific
24 ovarian subtypes and their most commonly referred

1 genetic information or genetic predis- --

2 sorry -- mutated genes. So I'm -- that's right.

3 Q Okay.

4 A They are -- they are similar in that
5 both are, again, introducing factual information
6 about the current knowledge in ovarian cancer in
7 this literature, again pointing out that
8 referencing the papers that they both came from,
9 being the Nunes as well as the appropriate
10 references.

11 Q Okay. And, then, the paragraph below
12 that starts endo- -- "endometrioid carcinoma,"
13 paren, "(EC)." Correct?

14 A Correct.

15 Q If we look --

16 And then that goes all the way to the
17 word "mucin-coding genes" with two citations;
18 correct?

19 A Correct.

20 Q If we look at 2 and the top of page 3
21 in Nunes, there's a sentence that starts "EC."
22 It does not spell out endometrioid carcinoma. Do
23 you see that four lines from the top? I'm sorry.
24 Four lines from the bottom --

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1 MS. O'DELL:

2 I'm sorry.

3 MR. FERGUSON:

4 Q -- on page 2.

5 A Yes.

6 MR. FERGUSON:

7 Sorry. Leigh, it's on page -- the
8 bottom of page 2.

9 MS. O'DELL:

10 Oh, I'm there. When you said the top,
11 I got --

12 MR. FERGUSON:

13 No worries. That's -- my mistake.

14 Q Okay. It says "EC subtypes," and then
15 it goes to mucin-coding genes on the top of page
16 3. Correct?

17 A Correct.

18 Q Again, that paragraph is nearly
19 identical to the one in your report. Correct?

20 MS. O'DELL:

21 Object to the form.

22 MR. FERGUSON:

23 Q Same word, same order, same citations;
24 correct?

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1 MS. O'DELL:

2 Object to the form.

3 A So my -- my report is similar to the
4 review article. It -- it's listing the subtypes
5 of ovarian cancer and -- based on the Nunes
6 paper, which is a 2018 publication, so a more
7 current review. I'm, again, providing that
8 referenced information about the -- the -- this
9 observation.

10 Q You're citing the same references as
11 Nunes; correct?

12 A Yes.

13 Q You cite the -- the various gene --
14 expression of gene in the same order they do,
15 so --

16 Correct?

17 A Yes.

18 Q And is that just coincidental? That's
19 just happened? You happened to have put this
20 paragraph in the same order with the same
21 notations as -- as Nunes?

22 MS. O'DELL:

23 Object to the form.

24 A Well, I'm listing the same information

1 that's contained in the Nunes paper. And seeing
2 as that -- this was a review of the literature
3 with -- you know, based on the state of the art,
4 the Nunes review is exactly that. And, again,
5 I'm -- I'm repeating the information regarding
6 the specific gene information as it relates to
7 this -- this ovarian cancer risk and -- and --
8 and, again, appropriately citing the basic
9 studies as Nunes did.

10 MR. FERGUSON:

11 Q With virtually the same wording?

12 A With similar wording, yes.

13 Q Let's look at page -- page 7.

14 MS. O'DELL:

15 His report?

16 MR. FERGUSON:

17 Q Yeah. I apologize. Your report.

18 We can set Nunes aside now.

19 You have a paragraph starts -- that
20 starts "individuals can inherit mutations in
21 BRCA1, BRCA2 or p53."

22 See it?

23 A Uh-huh.

24 Q And you say, "These defects allow

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1 additional mutations to accumulate in cells and
2 lead to a higher probability of cells being
3 cancerous."

4 Correct?

5 A Correct.

6 Q And you've indicated earlier in your
7 report that cancer is caused by mutations.

8 Correct?

9 A Correct.

10 Q And you say here that mutations in
11 BRCA1, BRCA2 or p53 can result in the
12 accumulation of additional mutations in cells.

13 Correct?

14 MS. O'DELL:

15 Object to the form.

16 A Yeah. I made the statement that BRCA1,
17 BRCA2 and p53, they can be inherited and then, in
18 turn, positive for those gene mutations.

19 MR. FERGUSON:

20 Q Okay. Would you --

21 A So I guess if you could ask the
22 question again to make sure I understand it.

23 Q Well, let me -- doesn't this paragraph
24 mean, in your comments here, that BRCA1, BRCA2,

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1 or p53 mutations can be considered causes of
2 cancer?

3 MS. O'DELL:

4 Object to the form.

5 A No. Not -- not specifically causal. I
6 think the -- each of these -- as we've discussed,
7 each of these genes, BRCA1 and BRCA2, or starting
8 with BRCA1 and BRCA2, increase the probability of
9 a -- of a person -- generally women -- getting
10 breast or ovarian cancer but do not exclusively
11 mean somebody with that mutation will get cancer.

12 So, with that knowledge, I would not
13 consider BRCA1 and BRCA2 mutation alone
14 sufficient to cause cancer. It increased the
15 risk.

16 And, as we talked about, p53 is a bit
17 more of a higher-risk gene, and the question as
18 to whether or not it is possible for someone to
19 have a -- what the rate of someone having a p53
20 mutation and not getting cancer, I believe, is
21 currently unknown. But there, again, is a much
22 higher probability of developing -- developing
23 cancer.

24 MR. FERGUSON:

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1 Q And then the last line there of page 7,
2 you say, "The lifetime risk for ovarian cancer is
3 approximately 40 percent for BRCA1 carriers and
4 15 to 20 percent for BRCA2 carriers."

5 Correct?

6 A Correct. Based on -- based on the
7 study that I referenced, yes.

8 Q Right.

9 And -- and the -- the -- if we look at
10 the increased risk of 40 percent as compared to
11 the risk of cancer in the -- of ovarian cancer in
12 the general population, that's a 25-fold increase
13 for BRCA1 and about a 7- or 8-fold increase for
14 BRCA2; correct?

15 MS. O'DELL:

16 Object to the form.

17 A I -- I would have to -- to determine
18 that. But I would say so. I'm certainly
19 comfortable stating that the lifetime risk for
20 ovarian cancer is approximately 40 percent. I'd
21 have to verify your -- your math about that
22 indicating a 25-fold increase.

23 MR. FERGUSON:

24 Q Do you know what the rate in the

1 general population of ovarian cancer is?

2 A It's fairly low. If I -- thinking of
3 the cohort studies that were reviewed as part of
4 this, it was roughly a hundred to 200 cases per
5 30- to 40,000 women in those -- in those studies,
6 so relatively low.

7 Q And if we go to the top of the next
8 page, you say -- it's page 8 -- "Therefore, the
9 presence of mutations in the BRCA genes do not
10 guarantee that carriers will get cancer. The
11 presence of these mutations increases a person's
12 risk of developing cancer when exposed to a
13 carcinogen."

14 Correct?

15 A Correct.

16 Q And you cite Park, Vitonis, and Wu for
17 that. Is that correct?

18 A That's correct.

19 Q Looking at Park, isn't it true that
20 Park does not supply any evidence to support your
21 claim that mutations in BRCA1, BRCA2 and/or p53
22 increase a person's risk of developing cancer
23 when exposed to a carcinogen?

24 A I'd have to remind myself of what's in

1 Park.

2 Q Are you going through the entirety of
3 the article?

4 A I'm just reminding myself the content
5 to see if I could find something that was
6 specifically related to your question about the
7 presence of a BRCA1 or 2 mutation.

8 Q Okay. Is the BRCA1, BRCA2, p53, any of
9 those even mentioned in the article?

10 And -- and I'm not sure we'll have time
11 for you to go through each one of them in this
12 much --

13 You've got -- you cited them for these
14 propositions. I'm trying to ask you why you
15 cited them for this proposition.

16 A I -- I'd have to look in more detail.
17 I don't have a specific answer regarding the --
18 regarding BRCA1 --

19 Q Okay.

20 A -- I'm sorry -- BRCA genes.

21 I would suspect the Park reference was
22 more in the discussion of overall relative risk
23 of developing cancer and not necessarily
24 exclusive to the presence of a mutation.

1 So the -- the Park paper does discuss
2 the relationship of ovarian cancer risk relative
3 to benign gynecological conditions.

4 Q And -- and your comment that you've
5 cited these studies for is the presence of these
6 mutations increases a person's risk of developing
7 cancer when exposed to a carcinogen. And these
8 mutations would be what you've been talking about
9 in this paragraph, the B -- the BRCA1, BRCA2, and
10 p53; correct?

11 MS. O'DELL:

12 Object to the form.

13 A The sentence is worded, "The presence
14 of these mutations increases a person's risk of
15 developing cancer when exposed to a carcinogen."

16 MR. FERGUSON:

17 Q Right. Right.

18 And, for example, in Vitonis, isn't it
19 true that BRCA1, BRCA2 and p53 were not even
20 determined in that study and, instead, Jewish
21 ethnicity was used as a surrogate for a woman's
22 risk of having a mutation in one of these genes?

23 Do you recall that --

24 A Again, I would have --

1 Q -- one way or the other?

2 MS. O'DELL:

3 Objection.

4 A I would have to review the -- review
5 the paper. Because part of the review is to
6 be -- include appropriate references with regards
7 to ovarian cancer risk, and those may -- I think
8 those publications provide some information in
9 that space.

10 MR. FERGUSON:

11 Q All right. But when you cite studies
12 for a statement in your report, shouldn't the
13 studies relate to that statement?

14 MS. O'DELL:

15 Object to the form.

16 A Well, the studies relate to a person's
17 risk of developing cancer. But I -- I think
18 it -- it doesn't change the accuracy of the
19 presence of the mutation relative to that risk.
20 But the -- I don't have a -- a good answer as far
21 as relationship of BRCA1 and 2 to the Park paper.

22 MR. FERGUSON:

23 Q And -- and, then --

24 Well, we talked about Vitonis, too.

1 And then let's get to Wu.

2 MS. O'DELL:

3 Object to the form. You didn't comment
4 specifically about Vitonis, if you've got an
5 issue with Vitonis. You know, it's not fair to
6 assume that because I don't think you asked a
7 direct question.

8 MR. FERGUSON:

9 Okay. I thought I did, but I could be
10 mistaken.

11 MS. O'DELL:

12 You mentioned it, but I don't think
13 you -- I think it was more you rather than asking
14 a question.

15 MR. FERGUSON:

16 Q With regard to Wu, do you recall that,
17 in Wu, BRCA1, BRCA2, and p53 inherited carrier
18 mutation status were not even determined in that
19 study? Do you recall that --

20 A The --

21 Q -- one way or the other?

22 MS. O'DELL:

23 Object to the form.

24 A The Wu paper specifically discussed

1 nongenetic risk factors.

2 MR. FERGUSON:

3 Q Let's go to the next paragraph, and
4 there you talk about single nucleotide variance,
5 SNVs; correct?

6 A Towards the bottom of the paragraph.
7 As -- in terms of modifiers, yes.

8 Q Yeah. Are -- are single nucleotide
9 variants mutations?

10 A Yes.

11 Q Do most SNVs result in functionally
12 defective proteins?

13 A Statistically speaking on a genome-wide
14 basis, no.

15 So a -- a single nucleotide variant is
16 a variant at any point. And if we consider
17 statistically that about 1 percent of the genome
18 encodes proteins, again, it's statistically less
19 likely that any SNV would affect a protein.

20 Q Okay. Let's look at the next
21 paragraph. There you talk about Lynch syndrome;
22 correct?

23 A Correct.

24 Q And you make a statement that Lynch

1 syndrome patients have an increased risk of
2 cancer when exposed to a carcinogen. Correct?

3 A Correct.

4 Q What carcinogens are you referring to?

5 A I'm not -- not referring to a specific
6 carcinogen. I'm using the term "carcinogen" to
7 refer to an insult that would result in DNA
8 damage specifically because, similar to the BRCA
9 mutations, Lynch syndrome impairs DNA mismatch
10 repair.

11 So that defect alone is not sufficient
12 to result in a cellular transformation, so
13 something else has to occur. And when we
14 consider that carcinogens are -- the term
15 "carcinogen" generally refers to something that
16 has the potential to damage cellular components
17 or DNA, it's putting the --

18 Inability to repair along with the
19 presence of a carcinogen is where that sentence
20 comes from.

21 Q So -- and I want to make sure I
22 understand what you're saying. Are you saying
23 that Lynch syndrome patients have an increased
24 risk of developing cancer after exposure to a

1 carcinogen, just like everyone else?

2 A No. I'm stating that Lynch syndrome --

3 MS. O'DELL:

4 Object to the form. Excuse me.

5 A Lynch syndrome is a hereditary
6 condition that increases the overall risk of
7 cancer to an individual, similar to BRCA1 and 2
8 mutation.

9 MR. FERGUSON:

10 Q So you -- are you claiming that Lynch
11 syndrome patients have a greater increase in
12 relative risk when exposed to a particular
13 carcinogen than do people without Lynch syndrome?

14 MS. O'DELL:

15 Object to the form.

16 A No, I'm not making that statement, to a
17 specific carcinogen.

18 MR. FERGUSON:

19 Q In your next paragraph you talk of --
20 you start with "Myriad Genetics," and you say,
21 "As with all inherited traits, a positive family
22 history is the strongest indicator of the
23 presence of genetic risk alleles in an
24 individual."

1 Correct?

2 A Correct.

3 Q Isn't it true that many women who have
4 inherited mutations like BRCA1 or BRCA2 and genes
5 that predispose to ovarian cancer development do
6 not have a family history of breast or ovarian
7 cancer?

8 A So the -- your -- your question is a
9 little bit different than the statement. So
10 the -- if I could clarify the statement in the
11 report, it is more that a positive family history
12 would be a likely indicator that someone has a
13 genetic risk variant such as BRCA1 and 2.

14 Q Isn't it true that family history is
15 not a sensitive or specific indicator of
16 whether -- of whether a particular woman has
17 inherited a mutation in a gene associated with
18 increased risk of ovarian cancer?

19 MS. O'DELL:

20 Object to the form.

21 A I would say that family -- I would ask
22 to define "sensitive" or "specific," because in
23 genetics overall, family history remains a
24 valuable and important characteristic in terms of

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1 determining the genetic component of -- of any
2 disease, cancer included. And, so, if there's
3 something exact regarding its sensitivity or
4 specificity that I can comment on, I will if I
5 know the answer. But...

6 MR. FERGUSON:

7 Q In -- in the top of the page -- of
8 page 9, the next page, you indicate, "Because of
9 the large number of individuals tested and the
10 ability to trace their genetic inheritance, the
11 genes involved in cancer development are well
12 established."

13 Is that correct?

14 A Correct. That's what I state. I did
15 make that statement.

16 Q And given that they're well
17 established, can you name all of the inherited
18 genes that have been identified as being
19 associated with an increased risk of ovarian
20 cancer?

21 A No, not -- I can't name them all off
22 the top of my head, no. There's something in the
23 neighborhood of 500 to -- 500 genes of strong
24 association of cancer risk and progression, some

1 number higher than that if you're looking at
2 indirect or genetic complex formation.

3 You know, depends how far down the
4 cellular control and signal transduction and
5 growth and proliferation road that we go as far
6 as how many genes. But I'm sure, as everyone
7 well appreciates, everything in biology is
8 interrelated in some form.

9 And, so, it -- but I would say this
10 statement here is that our ability to look at
11 large-scale genetic analysis in individuals of a
12 variety of cancer types, given the number of
13 individuals affected by cancer and the analysis
14 of their genetics, we've been able to identify
15 many of -- many of the fundamental or most --
16 perhaps most of the fundamental genes involved in
17 that initial disease initiation or progression.

18 It's important that it is not a
19 comprehensive list. Hence, it is not "all," but
20 there are a large number of genes that are well
21 established.

22 Q Okay. Let's look at the next page, 10.
23 And you have a paragraph that starts
24 "Macrophages."

1 A Uh-huh.

2 Q And the last sentence says, "Generally
3 speaking, macrophages can increase inflammation
4 or decrease inflammation, depending on the
5 cytokines released."

6 Correct?

7 A Correct.

8 Q So, with that statement, do you agree
9 that inflammation can have both protumorigenic
10 and antitumorigenic effects, depending on
11 context, just as you state here for macrophages?

12 MS. O'DELL:

13 Object to the form.

14 A No, I -- I would not agree with that.
15 I -- I don't know of any evidence of that, that
16 inflammation, as a physiological phenomenon, acts
17 as an antitumor effect.

18 MR. FERGUSON:

19 Q Going to the next page, the page 11 --
20 I'm trying to get through this
21 hopefully within the next 15 minutes.

22 -- under the role of inflammation in
23 ovarian cancer --

24 Are you with me there?

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1 A I am.

2 Q And you're obviously talking about the
3 role of inflammation there. Isn't it true that
4 no published animal model has ever shown that
5 inducing inflammation induces the development of
6 ovarian cancer?

7 MS. O'DELL:

8 Object to the form.

9 A We've been -- earlier today we were
10 discussing some animal models as it relates to --

11 MR. FERGUSON:

12 Q Yeah. You and Miss Brown talked about
13 a number of animal models.

14 A Yeah.

15 Q And -- and what I'm trying to ask you,
16 is there any of those animal models or any others
17 that have ever shown that inducing inflammation
18 induces the development of ovarian cancer?

19 A I didn't -- I didn't look specifically
20 for an animal study of that type in the process
21 of developing the report.

22 Q Later down that page, you talk about
23 two models. "The literature reviews as well as
24 many direct studies feature the immune system as

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1 being an important mediator of ovarian
2 carcinogenesis via two models, chronic
3 inflammation and incessant ovulation."

4 Correct?

5 A Correct.

6 Q Is it your opinion that incessant
7 ovulation is a form of chronic inflammation?

8 A It is not.

9 Q Isn't it true that there's no
10 pathological evidence in humans that perineal
11 talc users have ovarian inflammation?

12 MS. O'DELL:

13 Object to the form.

14 A I'm thinking.

15 I would have to review the --

16 I'm sorry. That's -- it's --

17 MR. FERGUSON:

18 Q Okay.

19 A I would -- again, I would have to look
20 more carefully for that. I can't -- I can't name
21 a study of that type right now.

22 Q So I think you've said previously --

23 Are you done looking?

24 I understood you couldn't give me

1 anything on that, so that's -- that's fine.

2 Let's move on.

3 A Okay.

4 Q I think you've stated earlier that your
5 opinion in this case is based on the totality of
6 what is included in the product, the talcum
7 powder products. Is that correct?

8 A Correct.

9 Q So you're -- you cannot distinguish
10 the -- the carcinogenicity of the constituent
11 parts of the talcum powder products, correct,
12 including the fragrance?

13 MS. O'DELL:

14 Object to the form.

15 A I -- I was -- I was not asked to -- to
16 provide that delineation. And, so, instead,
17 subsequent to seeing some of the other expert
18 reports, we began with talcum powder as a product
19 and then have since learned more about the
20 constituent components, including asbestos,
21 fragrance, potential for heavy metals, which I
22 understand or I've observed that there's a
23 variety of testing documents that -- that show a
24 variety of results.

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1 So, to answer your question, I did not
2 specifically evaluate the individual specific
3 components in any -- in any individual product as
4 it relates. Instead, remained focused on the
5 mechanism for the complete -- complete product.

6 MR. FERGUSON:

7 Q And you've made reference to heavy
8 metals throughout your testimony on occasion. Do
9 you recall that?

10 A I do.

11 Q Do you have any opinions that any of
12 these heavy metals contribute to the inflammation
13 process that you've been talking about?

14 A The -- to the inflammation --

15 I'm not aware of any direct evidence
16 for heavy metal contribution to the inflammation
17 process that we've been discussing. Instead, the
18 heavy metals, particularly chromium, caught my
19 attention because of its well-established ability
20 to directly damage DNA and, therefore, you know,
21 potentially play a role in carcinogenesis.

22 Q Do you have any knowledge or opinion
23 about how much chromium you claim is in the -- in
24 the body powder products?

1 MS. O'DELL:

2 Object to the form.

3 A I wasn't asked to evaluate the amount
4 of chromium or whether it was sufficient for
5 damage. It was more reviewing. I would have to
6 defer to other experts who have done the testing
7 on the products.

8 MR. FERGUSON:

9 Q So you have no opinion on that?

10 MS. O'DELL:

11 Object to the form.

12 A I'm sorry. An opinion on the amount of
13 chromium?

14 MR. FERGUSON:

15 Q Correct.

16 A Again, I wasn't asked to generate such
17 an opinion.

18 Q I think -- I think I'm almost done.

19 Isn't it true that published data have
20 demonstrated that talc is not genotoxic and does
21 not cause mutations?

22 MS. O'DELL:

23 Object to the form.

24 A I'm not aware of a study that

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1 specifically looked at the genotoxicity of -- of
2 talc. And I think it would certainly warrant
3 defining which type of talc and components
4 therein. But I'm -- I'm not aware of a study
5 that has concluded that there are no genotoxic
6 effects of any type of talc.

7 MR. FERGUSON:

8 Q Would you agree there's no evidence
9 that talc causes sister chromatid exchange or
10 unscheduled DNA synthesis?

11 MS. O'DELL:

12 Object to the form.

13 A I didn't -- I didn't review the
14 literature for those two specific phenomenon. I
15 would have to, again, specifically look or review
16 for that.

17 MR. FERGUSON:

18 Q So, as you sit here, you have no
19 opinion as to whether talc is or is not
20 mutagenic?

21 MS. O'DELL:

22 Object to the form.

23 A No. We've -- so talc in general,
24 particularly in its -- in its form of fibrous

1 talc with asbestiform bodies, I think would be
2 very reasonable to state that it has mutagenic
3 properties.

4 MR. FERGUSON:

5 Q And can you cite me any literature for
6 that?

7 A I would simply refer to the -- much of
8 the body of asbestos literature for the -- for
9 that.

10 MR. FERGUSON:

11 I think that's all I have. I'll turn
12 it over to someone else to ask some questions.

13 MS. BROWN:

14 Anybody with some more?

15 MS. O'DELL:

16 I'm going to take a break for a few
17 minutes.

18 VIDEOGRAPHER:

19 Going off the record. The time is
20 4:54 p.m.

21 (OFF THE RECORD.)

22 VIDEOGRAPHER:

23 We're back on the record. The time is
24 5:20 p.m.

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1 EXAMINATION

2 BY MS. O'DELL:

3 Q Dr. Levy, I have just a few follow-up
4 questions for you.

5 I'm gonna ask you to turn to page 14 of
6 your report.

7 And earlier today --

8 I'm going to ask, Doctor, if you could
9 put the exhibits in front of you, and we'll pull
10 those out.

11 But earlier today you were asked about
12 a letter from the FDA that was marked as Exhibit
13 Number 16, and if you could pull that out of your
14 stack there. And, specifically, if you'll turn
15 to page 4 of the letter.

16 And you'll recall that this letter was
17 written in 2014. Do you remember that?

18 A Yes.

19 Q And if you look, however, at page 4 of
20 the letter, it appears that the FDA's review of
21 the relevant toxicity literature stopped at the
22 year 2008. Fair?

23 MS. BROWN:

24 Objection to the form.

1 MS. O'DELL:

2 Q Did the FDA's review of the toxicity
3 literature stop in 2008?

4 A Yes.

5 Q And if you look at page 14 of -- of
6 your report, your review of the literature
7 included multiple references that were published
8 after 2008?

9 MS. BROWN:

10 Form.

11 A That's correct.

12 MS. O'DELL:

13 Q And, in fact, you cited Shukla that was
14 published in --

15 Was Shukla published in 2009?

16 A Yes. The reference is in the report to
17 2009.

18 Q Yes.

19 And, in addition to that, did you cite
20 other references in support of your opinion that
21 talc powder causes inflammation that were dated
22 and published after 2008?

23 A I did.

24 Q And, so, the suggestion by counsel for

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1 Johnson & Johnson that somehow the FDA had
2 reviewed the literature for toxicity up until the
3 date of this letter would have been incorrect?

4 MS. BROWN:

5 Objection to the form of the question.

6 A As -- as we discussed, the -- the
7 letter from the FDA dated April 1st, 2014, states
8 to include literature from 1980 to 2008.

9 MS. O'DELL:

10 Q Let me ask you --

11 You can put that aside, Dr. Levy.

12 Thank you.

13 And I want to ask you to pull out of
14 the stack the Exhibit 17, which is the Buz'Zard
15 paper.

16 A I have it.

17 Q And if you'll turn to page 581.

18 A Okay.

19 Q And just to orient our discussion,
20 counsel for Johnson & Johnson suggested that --
21 that this paper showed a decrease in reaction or
22 reactive oxygen species at the longest time
23 interval. Do you recall that discussion?

24 MS. BROWN:

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1 Objection to the form of the question.

2 A Yes, we -- we had a discussion
3 regarding the results shown in Figure 3, the
4 level of exposure of talc as well as its
5 duration. Sorry. The talc dose as well as
6 duration.

7 MS. O'DELL:

8 Q And in the -- if you'll look at
9 Figure 1, Doctor, explain to us, please, what
10 Figure 1 describes in terms of the viability of
11 the cells at the 72-hour mark.

12 A So the -- so Figure 1 is a graph
13 describing percent cell viability versus the
14 different normal or variant cells at a 24-hour
15 and 72-hour time point, two different ovarian
16 cancer cell lines, as well as doses of talc from
17 zero micrograms per milliliter up to 500
18 micrograms per milliliter, and each of those is
19 applied.

20 And at the 72-hour time point in both
21 cell lines, OSE2a and GCA1 -- GC1a shows a
22 decrease in cellular viability that is
23 dose-dependent in each of the four cell lines.

24 Q Okay. And --

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1 A Sorry. Each of the two cell lines.

2 Q And is it fair to say that the reason
3 you don't see dose response, you know, at the --
4 at the greatest magnitude is because the cells
5 essentially die?

6 MS. BROWN:

7 Objection to the form.

8 A Well, I would say if we consider the
9 results displayed in Figure 1 in relation to the
10 results displayed in Figure 3, an ex- -- an
11 explanation for the concentrating on the 500 --
12 the highest dose, the 500 micrograms per
13 milliliter, in the talc exposure, the decrease in
14 cellular viability is an -- is an explanation --
15 could be an explanation for the decrease in
16 reactive oxygen species.

17 MS. O'DELL:

18 Q Okay. Thank you, Doctor.

19 And if you'll put that aside and turn
20 to Exhibit 7, which was the Hamilton paper we
21 spent quite a lot of time on earlier.

22 Do you recall the -- that discussion
23 regarding the Hamilton paper?

24 A I do.

1 Q And what was the purpose for which you
2 cited the Hamilton paper?

3 A That it was one of the available animal
4 studies looking at the effects of talc on a rat
5 ovary.

6 Q And did the paper show that there was a
7 increase in inflammation as result of talc?

8 A Yes, in the form of foreign body
9 granulomas observed in five of the injected
10 ovaries.

11 Q And you're looking at, I guess, that
12 last sentence on page 103 and carrying over to
13 the -- to the narrative on page 105?

14 A Cellular foreign body?

15 Q Yes.

16 A Foreign body granulomas without any
17 surrounding inflammation were seen in five of the
18 injected ovaries. And similar lesions were not
19 uncommonly noted in the supracapsular fat in the
20 connective tissue matrix of the capsule.

21 Q And if you'll look down in the
22 discussion section, Dr. Levy, the first paragraph
23 there in your -- where -- beginning
24 "Unfortunately," does it appear that talc also

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1 induced fibrosis --

2 MS. BROWN:

3 Objection to form.

4 MS. O'DELL:

5 Q -- in the rats?

6 A The manuscript makes the statement
7 that, "Unfortunately, bursal distention occurred
8 as an unforeseen complication" and further states
9 that this probably resulted from talc-induced
10 fibrosis and obliteration of the small channel
11 which normally allows communication between the
12 cavity where the ovary lies and the perineum.

13 Q And though the authors concluded that
14 neoplastic changes were not seen, the authors did
15 find evidence of inflammation in their study?

16 A That's correct.

17 Q Prior to becoming involved in the
18 litigation, Dr. Levy, did you hold the opinion
19 that inflammation is a cause of cancer?

20 A As -- as we've discussed earlier, I
21 certainly held the opinion that, you know,
22 inflammation is a significant and necessary
23 component of cancer progression.

24 Q And has that been -- that general

1 principle been published in the peer-reviewed
2 literature?

3 A It has.

4 Q And, in regard to ovarian cancer, prior
5 to becoming involved in the litigation, did you
6 hold the opinion that inflammation was a part of
7 the development of ovarian cancer?

8 A Yes.

9 Q And has that been researched and that
10 research published in the peer-reviewed
11 literature?

12 A It has.

13 Q In the same way, has the fact that
14 talc, talcum powder, induces inflammation been
15 published in the peer-reviewed literature?

16 MS. BROWN:

17 Objection to the form.

18 A Yes.

19 MS. O'DELL:

20 Q And you were asked whether there was
21 evidence that talc caused inflammation in humans.
22 Do you recall that question?

23 A I do.

24 Q And based on your exhaustive review of

1 the literature, what evidence would you point to
2 undergirding your opinion that talc causes
3 inflammation in humans?

4 A I think considering the molecular
5 mechanism we were discussing of the recent paper
6 by Saed, et al., again, that we discussed earlier
7 today is a fairly in-depth set of experiments to
8 examine the specific inflammatory response
9 of -- of human cells to -- to talcum powder.

10 Q In addition to the Saed publications,
11 would you -- would you include the Shukla 2009
12 paper in your consideration of talc causing
13 inflammation in humans?

14 A Yes.

15 MS. BROWN:

16 Form.

17 MS. O'DELL:

18 Q You were asked about your methodology
19 numerous times today, and can -- would you
20 describe in -- in general the methodology you
21 have used in reaching your opinions in this case?

22 A Yes. To clarify or perhaps expand on
23 the earlier discussions, my methodology involved
24 a literature review to examine the totality of

1 the information available to the role that talcum
2 powder plays in inflammation in ovarian cancer.

3 And, so, that methodology involved,
4 first, a review of the literature and then a
5 development of a report and then a synthesis of a
6 biologically plausible mechanism where the basis
7 of that plausibility was to ask if each of the
8 different component steps that are described in
9 that mechanism was supported by peer-reviewed
10 research. First, does talc cause inflammation?
11 Second, does inflammation cause cancer? And
12 then, third -- or does inflammation cause ovarian
13 cancer? And then, third, is there -- is that
14 supportive of a overall mechanism of cancer
15 progression and metastasis?

16 Q Can that methodology be replicated?

17 A Certainly. I think, you know, anyone
18 with a similar -- similar background and
19 experience who -- who undertook the same
20 activities would likely -- certainly likely come
21 up with the same -- same conclusions.

22 Q Did you rely on the IARC monograph in
23 relation to nickel, chromium, and cobalt in
24 reaching your opinions in this case?

1 MS. BROWN:

2 Objection to the form.

3 A I -- so the -- the number of IARC
4 publications were certainly in the material that
5 was reviewed for -- for my -- for my report.

6 MS. O'DELL:

7 Q Based on your review of the literature,
8 is it your opinion that nickel causes
9 inflammation?

10 A Yes. The IARC -- the -- the
11 characterization of those compounds, nickel as
12 well as chromium, among others, are -- would have
13 an inflammatory response.

14 Q You were asked questions earlier
15 today -- actually, not so much earlier -- a few
16 minutes ago regarding the Park paper. And you
17 cited the Park paper on page -- I think it was 8
18 of your report.

19 A Yes.

20 Q And let me show you what I'm marking as
21 Exhibit 22 to your deposition.

22 (DEPOSITION EXHIBIT NUMBER 22
23 WAS MARKED FOR IDENTIFICATION.)

24 MS. O'DELL:

1 Q Is this the Park paper that you
2 referenced --

3 MS. BROWN:

4 Counsel, do you have a copy for us?

5 MS. O'DELL:

6 I don't. I'm assuming -- I don't think
7 Ken marked it, but I'm assuming he has a copy.

8 Q Is that the Park paper that you
9 referenced in your report, Dr. Levy?

10 A It is.

11 Q And if you'll turn to page 8 of the
12 paper, about midway down the first column, maybe
13 a little bit less, see the paragraph starting "We
14 did find an association"? Page 8.

15 A I'm looking for the page number.

16 Q Sorry. Let me give you a page number.
17 I'm not sure it has a page number.

18 A No, it doesn't.

19 Q Do you see the paragraph beginning "We
20 did find associations between overall cancer and
21 history of fibroid or ovarian cysts"? Do you see
22 that paragraph?

23 A Well, actually -- yes, I see that
24 paragraph.

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1 Q If you'll look further, the sentence
2 beginning "This observation may suggest," do you
3 see that?

4 A Yes. Uh-huh.

5 Q And the paper says, "This observation
6 may suggest a possible additive or synergistic
7 effect on tumor- -- tumorigenesis influenced by
8 the proinflammatory milieu from an increased
9 burden in the number of benign conditions.
10 Increased risk of serous cancer, ovarian cancer,
11 women with other proinflammatory risk factors has
12 been reported -- reported, most notably in talc
13 users."

14 Do you see that?

15 A I do.

16 Q Is that the section you were thinking
17 of when you cited it in your report?

18 MS. BROWN:

19 Objection to the form.

20 A Yes, it is.

21 MS. O'DELL:

22 Q Let me ask you to -- a couple of other
23 final questions, Dr. Levy.

24 Excuse me. Give me one moment.

1 In regard to opinions in relation to
2 the pathology of ovarian tissue, would you defer
3 to a gynecologist or gynecologic oncologist or a
4 pathologist regarding that matter?

5 A Yes, of course.

6 Q You testified earlier today that you
7 relied on the Longo testing in -- in reaching
8 your opinions in this case.

9 MS. BROWN:

10 Objection to the form.

11 MS. O'DELL:

12 Q Did you rely on Dr. Longo's testing
13 in -- in reaching your opinions in this case?

14 A Yes. They were -- they were one of
15 the -- among many of the manuscripts we've been
16 discussing.

17 Q Yeah.

18 In fact, you cite Dr. Longo's report on
19 page 15 of your report. Is that right?

20 MS. BROWN:

21 Objection to the form.

22 A Yes.

23 MS. O'DELL:

24 Q And -- and in terms of Dr. Longo's

1 report, his findings of 37 of 56 historical talc
2 samples being positive for asbestos and 41 of the
3 42 samples tested containing fibrous talc,
4 was -- was that information you had prior to
5 reaching your opinions and finalizing your
6 report?

7 MS. BROWN:

8 Objection to the form.

9 A Yes.

10 MS. O'DELL:

11 Q And in relation to Dr. Crowley's report
12 regarding the fragrance chemicals, do you defer
13 to Dr. Crowley regarding his analysis of the
14 fragrance chemicals?

15 A Yes.

16 Q And did you rely on the opinions he
17 reached in relation to the fragrance chemicals in
18 reaching your opinions in this case?

19 A Yes. My -- my review of that just, in
20 addition to deferring it, was -- just made the
21 general -- or made the statement that I was in
22 general agreement with his opinions in those
23 matters, seeing as that's not a -- not an area of
24 expertise of mine.

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1 Q And did you have the opportunity to
2 consider his report prior to finalizing your
3 report?

4 A I did.

5 Q I have nothing further. Thank you.

6 EXAMINATION

7 BY MS. BROWN:

8 Q Dr. Levy, would you take Exhibit 16
9 out, please, the FDA's response to the citizens
10 petition?

11 A I have it.

12 Q Counsel asked you some questions that
13 involved questions that I asked you. Remember
14 she asked you the lawyer for J & J didn't point
15 out the articles that were reviewed from 1980 to
16 2008 on page 4? Do you recall those questions
17 from plaintiffs' counsel?

18 A Yes.

19 Q Would you look at the last page of the
20 letter, page 6 of 7? I'd like to direct your
21 attention to the second sentence on this page
22 that begins "In consideration of your request."
23 Do you see that?

24 A I do.

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1 Q And it states, "In consideration of
2 your request, we conducted an expanded literature
3 search dating from the filing of the petition in
4 2008 through January 2014. The results of this
5 search failed to identify any new compelling
6 literature data or new scientific data."

7 Do you see that?

8 A I see that.

9 Q And putting together, then, the
10 information from page 4 and page 6, you see that
11 the FDA considered literature from 1980 to 2014.
12 Is that correct?

13 MS. O'DELL:

14 Object to the form.

15 A Yes, that is correct.

16 MS. BROWN:

17 Q And what the FDA concluded, contrary to
18 your opinion here, Doctor, is that a cogent
19 biological mechanism by which talc might lead to
20 ovarian cancer is lacking; correct?

21 MS. O'DELL:

22 Object to the form.

23 A That's in this --

24 MS. BROWN:

1 Q Directing your attention to page 4,
2 number 4, the conclusion regarding a cogent
3 biological mechanism lacking. Do you see that?

4 MS. O'DELL:

5 Object to the form.

6 A Yes. I see where they -- they made the
7 statement that cogent biological mechanism by
8 which talc might lead to ovarian cancer is
9 lacking and that exposure to talc does not
10 account for all cases of ovarian cancer.

11 MS. BROWN:

12 Q Next, Doctor, do you rely on the
13 findings of the Hamilton article in forming your
14 opinions in this case?

15 A Similar to as we've discussed, in a
16 portion, yes.

17 Q You, Dr. Levy, cannot point us to a
18 single paper showing an inflammatory response
19 leading to ovarian cancer in humans from talc
20 use. True?

21 A There is -- I do not know of a single
22 paper that -- in a controlled fashion in humans
23 provided talc exposure that then was --
24 subsequently led to cancer in humans. That's

1 correct.

2 Q Controlled aside, you're not aware of
3 any observational case report, any kind of study
4 that shows talcum powder use causing an
5 inflammatory response leading to cancer in
6 humans; correct?

7 MS. O'DELL:

8 Object to the form.

9 A I would -- my review and development of
10 the biological plausibly -- plausible mechanism
11 examined literature that led to the conclusions
12 described in the report. I'm not aware of a --

13 The human-based studies were all case
14 cohort and -- or case-controlled and cohort
15 studies that showed an association with talc
16 exposure and cancer, but I'm not aware of a
17 direct study.

18 MS. BROWN:

19 Q There have been some reports of alleged
20 findings of talc in tissues or in other parts of
21 the body. Are you familiar with those?

22 A Yes.

23 Q And you're not aware of any one of them
24 demonstrating an inflammatory response that the

1 talc was causing in the body. True?

2 MS. O'DELL:

3 Object to the form.

4 A I'm aware of a number of studies that
5 looked at inflammatory response in model systems
6 and cell lines, and additional studies that
7 looked at inflammation in humans I believe were
8 referenced.

9 Certainly the Penninkilampi manuscripts
10 described inflammatory observations and -- as
11 well as the Buz'Zard and Lau were on human cells.

12 Q Dr. Levy, is it your testimony that the
13 Penninkilampi meta-analysis of prior
14 case-controlled studies demonstrated a
15 inflammatory response of -- from perineal use of
16 talc that led to ovarian cancer?

17 MS. O'DELL:

18 Object to the form.

19 A No. That's not my statement. It was
20 that those -- those papers reported an
21 inflammatory observation as part of those
22 studies.

23 MS. BROWN:

24 Q Not in the tissue from talc; right,

1 Doctor?

2 MS. O'DELL:

3 Object to the form.

4 A It would be those studies in the meta
5 review were not examining the tissue content for
6 talc. So they're unable to make that
7 determination.

8 MS. BROWN:

9 Q So we must be missing. I'm -- what I'm
10 asking you is for any study at all in the whole
11 world that shows that talcum powder in somebody's
12 body causing an inflammatory response that led to
13 ovarian cancer. Can you name one?

14 MS. O'DELL:

15 Object to the form.

16 A I mean, we've -- we've discussed a
17 number of studies that described the risk and
18 association of talc in ovarian cancer. But the
19 limitation of the -- of your question or the
20 limitation of the studies relative to your
21 question is those particular studies may not have
22 also assessed the inflammatory response or an
23 inflammatory response, given the nature of the
24 studies.

1 MS. BROWN:

2 Q Well, we got one. We got the Heller
3 study that purported to find talc in ovarian
4 tissue; right?

5 MS. O'DELL:

6 Object to the form. Different --

7 MS. BROWN:

8 Counsel, it's form, please.

9 MS. O'DELL:

10 Object to the form.

11 A Yeah. What was the -- the Heller
12 study, here it is.

13 Yes, I recall our discussion of this
14 paper.

15 MS. BROWN:

16 Q Right.

17 And this study reported that there was
18 no inflammatory response around the talc that
19 they claimed to have found in the ovarian tissue.
20 True?

21 A They make those statements in the
22 paper, but the -- the -- I would have some
23 concern with the histological methods, but I
24 would certainly defer to a pathologist in the

1 sense of being able to determine the both
2 presence of talc and the inflammatory response in
3 that.

4 Q So you have some critiques of the
5 Heller study. Is that fair?

6 MS. O'DELL:

7 Object to the form.

8 A I would say I would need a -- I would
9 need a -- a -- I would need a further evaluation
10 of the methodology for detecting both talc as
11 well as inflammation in the same materials using
12 the methods of the Heller paper.

13 MS. BROWN:

14 Q Are you aware of any other paper that
15 you think is methodologically superior that shows
16 the presence of talc in ovarian tissue exhibiting
17 an inflammatory response?

18 MS. O'DELL:

19 Object to the form.

20 A Well, we've discussed the rat studies.

21 MS. BROWN:

22 Q Human tissue. That's my question.

23 A Human --

24 Q Human tissue.

1 MS. O'DELL:

2 Actually, that wasn't your question.

3 But you've clarified it, so --

4 A The -- so you're excluding -- are you
5 excluding cell lines?

6 MS. BROWN:

7 Q Yeah. Human beings. Do you know of
8 any study like Heller in human beings that
9 purports to find talc in human women ovarian
10 tissue that shows an inflammatory response?

11 MS. O'DELL:

12 Objection to form.

13 A I'm not aware of a study showing that
14 specifically.

15 MS. BROWN:

16 Q Counsel asked you some questions about
17 nickel causing inflammation that leads to ovarian
18 cancer. Do you recall those?

19 MS. O'DELL:

20 Object to the form.

21 A No. I was asked if -- if heavy
22 metal -- or components like nickel have been
23 shown to have a potential inflammatory response.

24 MS. BROWN:

1 Q Uh-huh. Because you're not aware of
2 any published scientific literature that shows
3 heavy metals cause inflamma- -- inflammation that
4 leads to ovarian cancer; right?

5 A I wasn't asked to -- to review for
6 that. I would state that there's a number of
7 studies that show the role of metals --
8 particularly chromium -- and its -- and its
9 damaging effect on DNA, which I think by -- would
10 certainly have both an inflammatory as well as
11 carcinogenic effect.

12 Q And we're here on an issue of ovarian
13 cancer. And, as it relates to ovarian cancer,
14 you're not aware of any scientific support for
15 the proposition that heavy metals can lead to
16 inflammation that causes ovarian cancer. Fair
17 enough?

18 A Well, I was -- certainly, I was asked
19 to review the literature to develop a -- and
20 develop conclusions of that literature as it
21 related to a -- a potential or possible
22 biological mechanism.

23 In doing that, in part of that review,
24 we certainly made the observation that talc and

1 its components, as we discussed earlier, may
2 have -- there's the possibility of having
3 additional component effects, such as heavy
4 metals and their effects, asbestiforms and their
5 effects and the like; therefore, really
6 considering the complete components of the
7 product overall.

8 Q And, as it relates to the testimony you
9 just gave, you're talking about just a
10 theoretical possibility; right?

11 MS. O'DELL:

12 Objection to form.

13 A Sure. And, then, from that review
14 developing a -- a conclusion of a biologically
15 plausible mechanism.

16 MS. BROWN:

17 Q Has that conclusion been published in
18 the peer-reviewed literature, Doctor?

19 A No, it has not.

20 Q And, in fact, as you -- all of the
21 opinions that you gave here today, those opinions
22 have not been published in the peer review
23 literature. True?

24 MS. O'DELL:

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1 Object to the form.

2 A Not at this time.

3 Q Counsel asked you some questions about
4 Dr. Longo. Do you recall that?

5 A Yes.

6 Q You've done nothing to validate the
7 findings that Dr. Longo writes about in his
8 reports. Is that fair?

9 A No, I have not done any experiments to
10 validate those findings.

11 Q Okay. Are you aware that some of the
12 samples that Dr. Longo tests and purports to find
13 asbestos were purchased off of eBay?

14 MS. O'DELL:

15 Misstates -- well --

16 A My review of the report, I was -- did
17 not include the -- I guess the specific history
18 of each of the samples.

19 MS. BROWN:

20 Q Do you understand that asbestos -- that
21 minerals like tremolite or anthophyllite, they
22 exist in both the asbestiform and nonasbestiform
23 way?

24 A I would defer to other experts on the

1 mineralogy of talc.

2 Q And whether what Dr. Longo is finding
3 in the samples that he tested is the asbestiform
4 or nonasbestiform variety of the minerals, you
5 would defer to others? Is that fair?

6 A I'd certainly defer to Dr. Longo.

7 Q And have you looked at any other
8 testing of the samples that Dr. Longo has tested?

9 MS. O'DELL:

10 Object to the form. Vague.

11 A Within the literature, there's -- there
12 was a number of tables describing testing,
13 described tests from previous testimony.

14 MS. BROWN:

15 Q Have you looked at the testing that
16 public health authorities like the FDA have done
17 on Johnson & Johnson's baby powder?

18 A I believe some of that was provided,
19 yes.

20 Q Are you relying on any finding of
21 asbestos from Dr. Longo in forming your opinions
22 here today?

23 A The --

24 MS. O'DELL:

1 Object to the form.

2 A The inclusion of the asbestos, again,
3 as -- as -- as we've discussed a few times today,
4 the conclusion I developed from the report were
5 not dependent or independent of any one or
6 another component of -- of the talcum powder.

7 As we discussed a bit ago, the presence
8 of asbestos as a known inflammatory mediator, as
9 well as potential carcinogen, I think just helps
10 lend additional support to the biological
11 plausibility of the mechanism. But I think that
12 biological mechanism is not dependent on the
13 presence of asbestos.

14 MS. BROWN:

15 Q Other than plaintiffs' expert,
16 Dr. Longo, are you relying on anything else to
17 support the potential for asbestos in baby
18 powder?

19 MS. O'DELL:

20 Object to the form.

21 A There's -- so I saw reference to
22 asbestos content in some of the other literature
23 that was reviewed during the time, and, so, there
24 were other publications that made mention of the

1 asbestos content in talc during the overall
2 review.

3 MS. BROWN:

4 Q Sitting here today, are you aware
5 whether or not that was Johnson & Johnson's
6 cosmetic talc?

7 MS. O'DELL:

8 Object to the form.

9 A I would have to look closely. I'm not
10 aware of that specifically.

11 MS. BROWN:

12 Q Counsel asked you some questions about
13 Dr. Crowley and whether or not you were relying
14 on the opinions he reached. Do you remember
15 those questions?

16 A I do.

17 Q What opinions did Dr. Crowley reach on
18 which you rely?

19 A Dr. Crowley performed an analysis of
20 the fragrance components and made assessments of
21 the individual chemical components and their
22 relationship to -- or I should say their -- their
23 inclusion on various lists for their -- their
24 chemical properties or safety. And in most -- in

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1 the majority of cases, the chemicals were not
2 listed. In a number of cases, there were large
3 numbers of chemicals listed as either irritants
4 and, therefore, able to cause inflammation, or,
5 in a few cases, as potential carcinogens.

6 And, so, it was that review of that
7 information, similar to our discussions around
8 asbestos, that I included or agreed with his
9 opinions regarding that on the last paragraph or
10 close to the last paragraph of the report that
11 stated I was just in agreement that these -- that
12 those chemicals contribute to the inflammatory
13 properties observed.

14 Q Do you know in what quantity the
15 chemicals Dr. Crowley identifies are present, if
16 at all, in Johnson & Johnson's products?

17 A No. I wasn't asked to provide that
18 review. I would defer to Dr. Crowley's report
19 regarding any quantitative analysis of those
20 chemicals.

21 Q And, as it relates to your opinion,
22 Dr. Levy, it makes no difference whether
23 Dr. Crowley's list has ten chemicals in
24 Quantity X or five chemicals in Quantity Y. Your

1 opinion is independent of Dr. Crowley's findings.

2 Is that fair?

3 MS. O'DELL:

4 Objection to form. Vague.

5 A Well, my -- my -- my opinion, again,
6 similar to -- as we've been discussing that, it
7 considers the totality of the information
8 available, including Dr. Crowley's report, but
9 does not rely on any one specific report or
10 otherwise.

11 And, so, the -- again, restating
12 similar to the asbestos, the presence of
13 potential irritants as another component in
14 the -- in the product just provides additional
15 support for that inflammatory mechanism playing a
16 significant role.

17 MS. BROWN:

18 Q If none of the chemicals Dr. Crowley
19 identified were present in baby powder, would you
20 hold the same opinion of biological plausibility?

21 A I would.

22 Q If no asbestos was present in baby
23 powder, would you hold the same opinion on
24 biological plausibility?

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1 A Yes.

2 MS. BROWN:

3 No further questions. Thank you.

4 MS. O'DELL:

5 I have just one follow-up.

6 Or do you have anything --

7 MR. FERGUSON:

8 Nothing further.

9 MS. O'DELL:

10 Excuse me. I'm sorry.

11 EXAMINATION

12 BY MS. O'DELL:

13 Q Dr. Crowley, are your opinions in this
14 case contained in your report as well as in the
15 testimony that you've given here today?

16 A You said Dr. Crowley.

17 Q Oh. Excuse me. Sorry. I had
18 Dr. Crowley on my mind.

19 Dr. Levy --

20 It's getting late in the day.

21 Dr. Levy, are your opinions in this
22 case expressed in your report and your testimony
23 today?

24 A Yes.

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1 Q And do you hold those opinions to a
2 reasonable degree of scientific certainty?

3 A Yes.

4 MS. O'DELL:

5 I have nothing further.

6 MS. BROWN:

7 Thanks for your time, Doctor.

8 I think we're off the record.

9 VIDEOGRAPHER:

10 We're off the record. The time is
11 6 p.m.

12 (Deposition concluded at 6:00 p.m.)

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1 C E R T I F I C A T E

2

3 I do hereby certify that the above and
4 foregoing transcript of proceedings in the matter
5 aforementioned was taken down by me in machine
6 shorthand, and the questions and answers thereto
7 were reduced to writing under my personal
8 supervision, and that the foregoing represents a
9 true and correct transcript of the proceedings
10 given by said witness upon said hearing.

11 I further certify that I am neither of
12 counsel nor of kin to the parties to the action,
13 nor am I in anywise interested in the result of
14 said cause.

15

16

17

18

19 LOIS ANNE ROBINSON, RPR, RMR
REGISTERED DIPLOMATE REPORTER
CERTIFIED REALTIME REPORTER

20

21

22

23

24

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1 E R R A T A P A G E

2

3 I, SHAWN LEVY, Ph.D., the witness herein,
have read the transcript of my testimony, and the
4 same is true and correct, to the best of my
knowledge, with the exceptions of the following
5 changes noted below, if any:

6 Page/Line Word(s) to be changed/reason Correct Word

7 _____

8 _____

9 _____

10 _____

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13 _____

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17 _____

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22 _____

23 SHAWN LEVY, Ph.D.

24

Exhibit 33

**UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY**

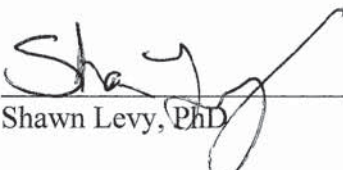
**IN RE JOHNSON & JOHNSON
TALCUM POWDER PRODUCTS
MARKETING, SALES PRACTICES,
AND PRODUCTS LIABILITY
LITIGATION**

MDL NO. 16-2738 (FLW) (LHG)

THIS DOCUMENT RELATES TO ALL CASES

**RULE 26 EXPERT REPORT OF
SHAWN LEVY, PHD**

Date: November 16, 2018


Shawn Levy, PhD

I. Qualifications and Background

I am a founding director of and a faculty investigator with the Genomic Services Laboratory at the HudsonAlpha Institute for Biotechnology. My focus is on use of high performance genotyping and sequencing technologies as support for plant and animal phylogenetic studies and translational and clinical-based projects. A portion of my research entails using whole-genome sequencing to identify genetic markers associated with specific health conditions.

I serve as executive director of the HudsonAlpha Clinical Services Laboratory, LLC, which I launched in 2014. I am adjunct faculty in the department of genetics and department of epidemiology at the University of Alabama at Birmingham, adjunct faculty in the department of biological Sciences at the University of Alabama at Huntsville, and serve as an ad hoc reviewer for scientific journals including Nature, Nature Genetics, Science, Cell, Genome Research and several others. I have been a co-chair of the Genomics Working Group of the American Medical Informatics Association, a community of scientists and health care professionals that work to facilitate collaboration and share knowledge across a continuum, from basic and applied research to the consumer and public health arenas.

Prior to joining HudsonAlpha in 2009, I was a faculty member at Vanderbilt University Medical Center with appointments in the Department of Molecular Physiology and Biophysics and the Department of Biomedical Informatics. I was the founding director of the Vanderbilt Microarray Shared Resource where I served as Director for 9 years. I received my PhD in biochemistry and completed a postdoctoral fellowship in genetics at Emory University in Atlanta, where I set up a microarray facility at the Emory Center for Molecular Medicine. My education, training, and experience are further set forth in my Curriculum Vitae (CV), which is attached to this report as **Exhibit A**.

As detailed in my CV, my research activities have examined a number of basic questions in human cancer such as the role of viral infection in head and neck cancer, the role of genetic mutation in risk for secondary cancer events following initial treatment, the genetics of B-cell

lymphoma, hepatosplenic T-cell lymphoma and malignant melanoma, and the role of STAT3 in triple-negative breast cancer. As the founding and Executive Director of the HudsonAlpha Clinical Services Laboratory, I also have interests and responsibilities in the clinical use of genetic testing for cancer risk and treatment stratification. HudsonAlpha launched the Information is Power campaign and has provided genetic testing for breast and ovarian cancer risk to women across the state of Alabama free of charge. My lab has also supported the Alabama Genomics Health Initiative that tests for genetic risks and carrier status for a number of diseases, including breast and ovarian cancer. This body of work in basic and clinical research in combination with earlier epidemiological work in the Shanghai Women's Health study provides the experience, education and expertise to develop this report.

I have been retained to describe the role of genetics in the pathogenesis of cancer in general and specifically ovarian cancer. Further, I have been asked to assess whether perineal use of talcum powder products induces a biologically plausible mechanism or mechanisms that result in ovarian cancer.

My report consists of a review and my conclusions regarding this cause-and-effect relationship. My opinions are based on my assessing and weighing the totality of the evidence, including relevant literature and available documentation, and my experience as a geneticist and scientific researcher. Report references are listed at the end of this report, and a more comprehensive list of the documents and materials reviewed prior to formulating the opinion in this report is attached as **Exhibit B**. The methodology that I have used to reach my opinions in this case is generally accepted in the scientific community and is the same methodology that I use in my research and other professional activities. All of my opinions stated below are held to a reasonable degree of scientific certainty. My opinions reflect my sole and independent judgment at the time of this report.

My billing rate is \$500 per hour. I have not testified by deposition or at trial during the last four years.

II. Cancer Overview

Cancer has become a descriptor that is ubiquitously used but describes an extremely complex and diverse collection of medical conditions. Cancer is also a word that represents an amazingly complicated and often misunderstood collection of diseases. At the most basic level, cancer can be described as a disease of unregulated cell growth but its simplicities end with that simple description. From the moment of conception until death, humans experience an unending cycle of cell growth, differentiation and death. As infants grow to children and then to adults, there are an array of growth processes that occur that represent the milestones of development and maturation. These processes are an orchestra of highly coordinated and regulated events with important checks and balances. When those highly regulated processes are defective or the checks and balances malfunction, the growth of the cells can become unregulated. Which tissue or cells become unregulated and exactly what process is defective defines the type of cancer and its progression. Cancer can be aggressive and highly metastatic when unregulated cells invade other parts of the body and destroy organs and tissues. Other types of cancer remain restricted to specific organs or cell types and may be less aggressive.

It is the DNA within our cells which provides the genetic code or instructions to create the cells, tissues, and organs that make a human. Subtle changes in that code lead to the diversity of people around the world, while more substantial changes in that code create the diversity of life forms around us, from the smallest bacteria to the largest plants and animals. All cells have one set of instructions that provides the information for cells to divide, tissues to grow and how cells should die.

III. The Role of Gene Mutations in the Development of Cancer

At its fundamental level, cancer is caused by changes (mutations) to the DNA within cells. The DNA that makes up our genetic code is organized into a large number of individual genes, each of which contains a specific subset of instructions telling the cell what functions to perform, as well as how to grow and divide. Errors in the instructions can cause the cell to stop its normal function and may allow a cell to become cancerous. Mutations that cause cancer most commonly

disrupt the regulation of the cell cycle (i.e., stages of cell growth and division). The following classifications of mutations are those most commonly found in cancer, but many other gene mutations can contribute to causing cancer as well.

Increasing cell growth and division. A gene mutation can initiate more rapid cell growth and division, resulting in many new cells that all have that same mutation. Proto-oncogenes are a group of genes that regulate cell growth, differentiation, division and death. When a proto-oncogene is mutated, it can become an oncogene that then instructs the cell to grow rapidly in an unregulated manner.

Loss of growth inhibition. A gene mutation can result in the renewed growth of a cell that had previously stopped growing. Normal cells regulate their division so that the human body contains the appropriate number of each type of cell. When the tumor suppressor genes that provide this inhibitory control become mutated, cells become cancer cells and continue to grow and amass. An example of one such gene is *p53*, which is discussed in more detail below.

Loss of DNA repair. Gene mutations can also affect the genes that proofread DNA and fix mutations before they can have a detrimental effect. DNA repair genes look for errors in a cell's DNA and make corrections. A mutation in a DNA repair gene may mean that other errors aren't corrected, leading cells to become cancerous through unchecked replication of damaged cells. Examples of DNA repair genes include *BRCA1* and *BRCA2* which are discussed in more detail below.

Another way of classifying gene mutations is by when they occur.

- 1) Inherited gene mutations: Inherited gene mutations are those mutations an individual is born with and that are present in all cells of the body. These types of mutations define traits and characteristics that have a family history. This type of mutation directly accounts for a small percentage of cancers. The indirect effects of this type of mutation is an area of active research. There are a growing number of genes and mutations that are known to increase the risk of cancer. *BRCA1* and *BRCA2* mutations and the increased risk for breast and ovarian cancer are two examples. While additional genes are being identified, the

percentage of individuals affected by mutations in those genes will be significantly less than those affected by *BRCA1* and *BRCA2*.

- 2) Acquired (somatic) gene mutations: Somatic mutations are acquired after birth. Most gene mutations that directly cause cancer occur after birth and aren't inherited. Gene mutations can be caused by a number of events or exposures. These include environmental exposures such as smoking, radiation, and cancer-causing chemicals (carcinogens). Biological and lifestyle exposures such as viruses, obesity, hormones, and chronic inflammation are also known to result in cancer-causing mutations. Each exposure type has its own mechanism in increasing risk for cancer. These mechanisms may be direct, such as radiation directly damaging DNA, as well as indirect, such as an external agent causing a cellular reaction or inflammatory response that then leads to DNA damage or mutation.

Both inherited and acquired gene mutations work together to cause cancer. While genetic testing has become commonplace for both assessing risk for cancer as well as directing treatment, the catalog of oncogenes, tumor suppressor genes, and DNA repair genes make genetic testing valuable and impactful for informing patients of their genetic risk for cancer. Genetic testing generally detects inherited mutations. Currently, genetic screening does not detect acquired gene mutations because they occur only in certain cells. Even if one has inherited a genetic mutation that predisposes one to cancer, that doesn't mean he or she is certain to get cancer. Rather, one or more additional gene mutations may be needed to cause cancer. The inherited gene mutation could instead make one more likely to develop cancer when exposed to a certain cancer-causing substance. Conversely, an individual may still develop cancer if they do not have mutations known to predispose one to cancer. Additionally, chemical and other environmental agents such as talcum powder products can interact with inherited mutations to cause ovarian cancer.

IV. The Role of Genetics in Ovarian Cancer

Ovarian cancer is the major cause of death from gynecologic disease and the second most common gynecologic malignancy worldwide (Nunes and Serpa, 2018; Siegel, 2015; Torre, 2015). The term "ovarian cancer" is often used to include fallopian tubal, ovarian epithelial and peritoneal

cancers since the pathogenesis, treatment and clinical courses are similar. Researchers now believe that most of these cancers originate in the distal portion of the fallopian tube (Levanon, 2008). The significant mortality is primarily associated with late diagnosis and resistance to therapy (Bowtell, 2010). Epithelial ovarian cancer (EOC) includes most malignant ovarian neoplasms (Chan, 2006) that can be classified based on morphologic and molecular genetic features into the following types: serous (OSC; low and high grade), endometrioid (EC), clear cell (OCCC) and mucinous (MC) carcinomas.

Certain specific genetic and transcriptional signatures are associated with each histological subtype. Low-grade OSC cases generally have genetic alterations in BRAF, KRAS, NRAS, and Erb-B2 Receptor Tyrosine Kinase 2 (ERBB2); high-grade OSC has mutations in Tumor Protein P53 (TP53), BRCA1/2, Neurofibromin 1 (NF1), RB Transcriptional Corepressor 1 (RB1), and Cyclin Dependent Kinase 12 (CDK12) (Chan, 2006). Homologous recombination repair of DNA damage is defective in approximately 50% of high-grade serous cancers along with alterations in signaling pathways such as PI3/Ras/Notch/ FoxM1 (Nunes and Serpa, 2018).

Endometrioid carcinoma (EC) subtypes involve mutations in AT-Rich Interaction Domain 1A (ARID1A), Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha (PI3KCA), Phosphatase And Tensin Homolog (PTEN), Protein Phosphatase 2 Scaffold Subunit Alpha (PPP2R1 α), and mismatch repair deficiency. Ovarian clear cell carcinoma (OCCC) subtypes have been found with de novo expression of HNF1 β (Mabuchi, 2009; Shen, 2013) as well as ARID1A, PI3KCA, PTEN, Catenin Beta 1 (CTNNB1) and PPP2R1 α mutations. MC comprises tumors with mutations in KRAS and a high frequency of ERBB2 amplification with overexpression of mucin-coding genes (Banerjee and Kaye, 2013; Jayson, 2014).

In addition to inherited mutations, exposure to the environment can result in DNA changes, or acquired gene mutations, that lead to cancer. These sources can be from exposure to minerals such as asbestos or arsenic, chemical exposures such as benzene or formaldehyde and from natural radiation sources like radon or ultraviolet light. These exposures constantly damage human DNA. Fortunately, cells have robust DNA repair mechanisms to ensure DNA damage is repaired before the DNA is replicated. These “proofreading” mechanisms react to DNA damage and stop DNA

replication. The mechanisms involve checkpoint control proteins such as the p53 protein, which acts to stop the cell cycle if DNA is damaged, and thus to suppress production of tumors. Cells that do not express functional p53 protein exhibit high rates of mutation in response to DNA damage, accelerating the formation of tumors.

BRCA1 and BRCA2 proteins also function in the DNA repair pathway. *BRCA1* and *BRCA2* are normally expressed in the cells of breast and other tissue, where they help repair damaged DNA, or destroy cells if DNA cannot be repaired. They are involved in the repair of chromosomal damage resulting from double-strand breaks. *BRCA1* combines with other tumor suppressors, DNA damage sensors and signal transducers to form a large multi-subunit protein complex known as the BRCA1-associated genome surveillance complex (BASC). *BRCA2* interacts with the RAD51 protein, also forming a complex that is vital for DNA repair.

Individuals can inherit mutations in *BRCA1*, *BRCA2* or *p53*,¹ and are termed “positive” for the gene mutation. Such mutations will detrimentally affect the ability to repair DNA or sense the presence of damaged DNA. These defects allow additional mutations to accumulate in cells and lead to a higher probability of cells becoming cancerous. *BRCA1*, *BRCA2* and *p53* mutations can also be acquired in certain cells. If those cells form a tumor, the cancerous tissue can be tested for these gene mutations.

BRCA mutations are inherited in an autosomal dominant fashion, meaning inheriting only one copy results in increased cancer risk. Some individuals with a mutation in the *BRCA1* or *BRCA2* gene will develop cancer during their lifetime, but others will not. Penetrance refers to the proportion of individuals with a genetic mutation who exhibit symptoms of the disorder. Where some carriers do not develop a disorder, as in the case of *BRCA* carriers, the condition is said to have incomplete penetrance. In such instances, additional genetic, environmental and lifestyle factors must be present for the disorder to manifest. The lifetime risk for ovarian cancer is approximately 40 percent for *BRCA1* carriers and 15 to 20 percent for *BRCA2* carriers (Berek et

¹ Genes consist of genetic information that code for functional proteins. Both the gene and the protein they code share the same alphanumeric name. To avoid confusion, genes are italicized in text and proteins are not. For example: *BRCA1* (gene) and BRCA1 (protein).

al., 2012; Paluch-Shimon et al., 2016). Therefore, the presence of mutations in the *BRCA* genes do not guarantee that carriers will get cancer. The presence of these mutations increases a person's risk of developing cancer when exposed to a carcinogen (Park, 2018; Vitonis, 2011; Wu, 2015).

Mutations in *BRCA* genes are found in the minority of epithelial ovarian cancer cases, suggesting additional mechanisms involving other genes that predispose women to ovarian cancer. The location of the mutation within the *BRCA1* and *BRCA2* genes has been associated with different ovarian cancer risk (Rebbeck, 2015). Additionally, several common alleles, or alternate forms of a gene, have been found to modify ovarian cancer risk for *BRCA1* and *BRCA2* mutation carriers. These modifier genes alter the process by which information from a gene is used to synthesize a final gene product (gene expression) in another gene, which in turn causes a disease. They are hypothesized to act as low to moderate penetrance alleles that contribute to ovarian cancer risk. (Barnes and Antoniou, 2012; Ramus, 2008; Saed, 2017; Sellers, 2008). These modifiers consist of changes in the DNA called single-nucleotide variants (SNVs), and result in a point mutation in the gene. The mutation can result in a structurally altered protein that is functionally defective. Some of the affected proteins are oxidants, antioxidants, or otherwise involved in regulatory pathways involving cancer risk, as discussed below.

Lynch syndrome is another hereditary condition that increases the risk of ovarian cancer. It is caused by mutations that impair DNA mismatch repair, and the disease is inherited in an autosomal dominant manner similar to *BRCA* mutations. As in the case of *BRCA* mutations, due to incomplete penetrance inheriting a Lynch-associated mutation does not guarantee an individual will get cancer, but rather, that the risk of cancer will increase when exposed to a carcinogen.

Myriad Genetics was an early pioneer in the development of commercial genetic testing for *BRCA1* and *BRCA2* mutations and predicting risk for breast and ovarian cancer. As with all inherited traits, a positive family history is the strongest indicator of the presence of genetic risk alleles in an individual. Since the exact identity of those risk alleles and the magnitude of cancer risk remain unknown until testing is performed, early guidelines for testing were based on a positive family history. The availability of testing has increased and costs of testing have fallen. However, genetic testing remains a relatively rare practice in the general population. Since the

early 1990s, advanced molecular biological technologies have allowed for the connection to be made between specific genetic mutations and the resulting hereditary cancers. Because of the large number of individuals tested and the ability to trace their genetic inheritance, the genes involved in cancer development are well established. In the overall spectrum, there are additional variants and genes with minor involvement, but development is dependent upon specific and complex interactions that occur in rare situations, and it is extremely unlikely any would have impact of known mutations such as *BRCA1* or *BRCA2*.

V. Response to Cellular Injury

As previously mentioned, from the moment of conception, the human body relies on continuous cell growth and development for normal health and function. Some tissues and cell types continually turn over. Our skin, blood cells, immune cells and the cells that line our digestive tract are examples where cells are continually growing and replacing older cells. In the case of an injury, a complex cascade of events begins which involves inflammation and culminates in the healing of the wound. During tissue injury, cell proliferation is enhanced while the tissue regenerates. After the healing is complete, proliferation and inflammation subside.

In contrast, proliferating cells that sustain DNA damage and/or mutagenic insult (for example, initiated cells) continue to proliferate in microenvironments rich in inflammatory cells and growth/survival factors that support their growth. In a sense, tumors act as wounds that fail to heal (Dvorak, 1986). Recent studies have shown a link between inflammation associated with wound healing and ovarian cancer cell seeding (Jia, 2018). In addition to inflammation, the innate immune response plays a role in promoting cancer development and progression. These observations are generally accepted in the scientific literature (Coussens and Werb, 2002; Pardoll, 2002).

VI. Inflammation

A. The Role of Inflammation in Cancer - General

The functional relationship of cancer and inflammation was first described in the mid-1800s. Rudolf Virchow noted leucocytes in neoplastic tissues in 1863 and made a connection between inflammation and cancer (as cited in Balkwill and Mantovani, 2001). He suggested that the "lymphoreticular infiltrate" reflected the origin of cancer at sites of chronic inflammation. Research published over the last 20 years has provided further understanding of the inflammatory microenvironment of malignant tissues and validates Virchow's hypothesis. Furthermore, the links between cancer and inflammation now have quite strong implications for prevention and treatment. (Balkwill and Mantovani, 2001).

Macrophages are versatile immune-system cells that play a variety of roles in health and well-being. They act in tissues and free-floating cells in the blood that engulf and digest cellular debris, foreign substances, infectious microbes, cancer cells and anything that does not have the correct cell surface proteins to indicate a healthy cell to the body. They take various forms with various names throughout the body and have specialized tasks, including recruiting other immune cells like lymphocytes to sites of infection or acting as antigen presenting cells to T cells. Upon activation by contact with substances foreign to the body, macrophages release small proteins called cytokines. Generally speaking, macrophages can increase inflammation or decrease inflammation depending on the cytokines released.

Tumor-associated macrophages (TAM) are a major component of the infiltrate of most, if not all, tumors (Franklin and Li, 2016). TAM derive from circulating monocytic precursors, and are directed into the tumor by chemoattractant cytokines called chemokines. Many tumor cells also produce cytokines called colony-stimulating factors that prolong survival of TAM. When appropriately activated, TAM can kill tumor cells or elicit tissue destructive reactions on the vascular endothelium to disrupt blood supply to the tumor. However, TAM also produce growth and angiogenic factors as well as protease enzymes which degrade the extracellular matrix. Therefore, TAM can stimulate tumor-cell proliferation, promote angiogenesis, and favor invasion and metastasis (Mantovani, 1992b; Mantovani, 1997). Direct evidence for the importance of

protease production by TAM, neutrophils, and mast cells during experimental carcinogenesis was reported more than 15 years ago (Coussens, 2000). Since that time, the report by Coussens et al. has been cited nearly 300 times by other studies. This dual potential of TAM has been described in the literature as the "macrophage balance." (Liu and Cao, 2015; Mantovani, 1992a).

B. The Role of Inflammation in Ovarian Cancer

Inflammation has also been shown to play a key role directly in epithelial ovarian cancer. This principle is generally accepted in the scientific community and very well reviewed in the scientific literature over the last decade, as the role of inflammation is common in many types of cancer. (Charbonneau, 2013; Kisielewski, 2013; Maccio and Madeddu, 2012; Mor, 2011; Pardoll, 2002; Pejovic and Nezhat, 2011; Shan and Liu, 2009). The literature reviews, as well as many direct studies, feature the immune system as being an important mediator of ovarian carcinogenesis via two models for its role in ovarian cancer: 1) chronic inflammation and 2) incessant ovulation.

- 1) Chronic Inflammation: The chronic inflammation model of carcinogenesis proposes that chronic exposures to external or endogenous triggers of immunity (such as known carcinogens) and the persistence of immune cells cause ovarian cancer. These inflammatory triggers cause injury to surrounding epithelium, damage DNA through the release of reactive oxygen species (ROS), or produce cytokines that promote proliferation (Saed, 2017). One environmental exposure shown to induce inflammation in animal models and human lungs is talcum powder (Wehner, 1994). Composed primarily of magnesium silicate, talc has been linked to ovarian cancer risk in a number of studies (Ness, 2000; Mills, 2004; Merritt, 2008; Wu, 2009; Rosenblatt, 2011; Wu, 2015; Penninkilampi, 2018).
- 2) Incessant Ovulation: As stated in (Charbonneau, 2013), incessant ovulation results in damage due to rupturing of the ovulating follicle, which traumatizes the ovarian surface causing an immediate inflammatory response and wound repair. Repeating this process of damage and epithelial proliferation to repair the wound increases the risk of malignant transformation. Epidemiologic studies beginning nearly 50 years ago have implicated increased number of ovulations as a risk factor for ovarian cancer (Mahdavi, 2006). In

contrast, decreased risk of (i.e., protection from) ovarian cancer has been associated with increased parity (Adami, 1994; Modan, 2001), oral contraceptive use (Narod, 1998), breast feeding (Jordan, 2012) and older age at first menses (Titus-Ernstoff, 2001). All of these protective factors impact the number of lifetime ovulations. One of these early studies from the late 1970's, which has been further substantiated by more recent investigations, found protective effects of "anovulatory time" by combining information on both increased oral contraceptive use and parity as well as age at first and last menses (Casagrande, 1979), supporting the theory of incessant ovulation as an underlying mechanism of carcinogenesis.

As a part of the inflammatory response, macrophages induce oxidative stress through production of reactive oxygen species (ROS) and reactive nitrogen species (RNS). Normally, oxidants and antioxidants maintain a balance wherein the amount of ROS does not overwhelm the ability of the body, and antioxidants, to regulate them. Free radicals such as ROS and RNS are highly reactive and adversely alter DNA, proteins, and lipids (which comprise cell membranes) to promote tumor development and progression, and many cancers arise from sites that are subject to chronic irritation, infection, or inflammation. Cancer cells persist in a pro-oxidant state where there is excess production and generation of ROS that allows for tumor initiation, promotion and progression.

The association between exposure to pathogens and chronic inflammation in tumor promotion and progression is further support of the generally understood principle that chronic inflammation plays a key role in the development of ovarian cancer. Examples of inflammatory conditions that are associated with ovarian cancer include endometriosis and pelvic inflammatory disease. Evidence strongly suggests that endometriosis is a pelvic inflammatory condition (Agic, 2006), and that inflammation explains the association between endometriosis and epithelial ovarian cancer (Ness, 2000). Studies have found a relationship between pelvic inflammatory disease and ovarian cancer risk (Lin, 2011; Merritt, 2008). Moreover, the effect of non-steroidal anti-inflammatory drugs (NSAIDs) to reduce the risk of ovarian cancer provides additional support. The earlier studies with a focus on NSAIDs were preliminary and results were somewhat

inconsistent (Bonovas, 2005; Merritt, 2008), but a recent pooled analysis examining 12 case-control studies found aspirin could reduce ovarian cancer risk by 20%-34% (Trabert, 2014).

Additional studies illustrate the potential protective effects of anti-inflammatory agents, including from unexpected drugs such as metformin. As reviewed in Reid, 2017, evidence supports a role for the anti-diabetic agent, metformin, in the prevention and treatment of multiple cancers (Li, 2011). Studies reviewed include a case-control study including 1,611 incident ovarian cancer cases performed using the UK-based General Practice Research Database (Bodmer, 2011). Long-term use (≥ 30 prescriptions) of metformin (and not sulfonylureas or insulin) was associated with a trend towards reduced risk with an odds ratio of 0.61. Though these results alone were not statistically significant, the reported observation that the anti-inflammatory agent, metformin, appears to decrease the risk of cancer, is additional evidence that inflammation is a primary mediator of ovarian cancer. (Irie, 2016).

Considering the well-established role that inflammation plays in cancer and the beneficial effects of anti-inflammatory compounds on cancer risk and progression, it is logical to examine the environmental factors that may directly lead to cancer or that may increase chronic inflammation and indirectly lead to cancer. The International Agency for Research on Cancer (IARC) has recognized for nearly thirty years that there is sufficient evidence to conclude human exposure to asbestos is a cause of ovarian cancer (IARC, 1987; IARC, 2012). Not surprisingly, human studies have reported asbestos fibers in ovaries (Heller, 1996; Langseth, 2007). Meta-analysis continues to support the conclusion that exposure to asbestos increases risk for ovarian cancer (Camargo et al., 2011).

C. Talcum Powder Products

A number of studies have been performed to examine the role of talcum powder use in the development of ovarian cancers. A comprehensive and recent meta-analysis by Penninkilampi found an association between perineal talc use and ovarian cancer, with a greater association after a higher number of lifetime applications (Penninkilampi and Eslick, 2017). The Penninkilampi study identified 24 case-control (13,421 cases) and three cohort studies (890 cases). Observational studies involving at least 50 cases of ovarian cancer were eligible for inclusion. Penninkilampi

analyzed the association between ovarian cancer and any perineal talc use. Included studies reported specific types of ovarian cancer, long-term (>10 year) talc use total lifetime applications, frequency and use of talc while also using diaphragms or sanitary napkins.

The Penninkilampi study found a consistent association between perineal talc use and ovarian cancer. Variation in the magnitude of the effect was found when considering study design and ovarian cancer subtype. Any perineal talc use was associated with increased risk of ovarian cancer (OR=1.31, 95%CI 1.24-1.39). Greater than 3,600 lifetime applications (OR=1.42, 95%CI 1.25-1.61) was slightly more associated with ovarian cancer than less than 3,600 applications (OR=1.32, 95%CI 1.15- 1.50).

In addition to epidemiological evidence, an *in vitro* experiment by Buz'Zard and Lau reported an increase in ROS generation, increased cell proliferation and neoplastic transformation (conversion into cancerous cells) in human ovarian cells treated with talcum powder (Buz'Zard and Lau, 2007). They also found talcum powder treatment increased the number of reactive oxygen species produced by polymorphonuclear neutrophils, inflammatory cells whose role is to release large quantities of reactive oxygen species in response to a variety of harmful foreign stimuli. Additional studies have also shown the effects of talc on the immune response (Hamilton, 1984; Keskin, 2009; NTP, 1993).

Some studies have suggested that the link between ovarian cancer and talcum powder product use may be influenced by a number of genes (Belotte, 2015; Fletcher, 2018^a; Gates, 2008; Shukla, 2009). Gates and colleagues found that women with certain genetic variants in glutathionine S-transferase M1 (GSTM1) and/or glutathionine S-transferase T1 (GSTT1) may have a higher risk of ovarian cancer associated with talc use (Gates, 2008). In a recently peer-reviewed and accepted abstract, Harper and Saed report a mechanism by which talc enhances the pro-oxidant state in normal (ovarian and tubal) and ovarian cancer cells, through induction of gene point mutations (corresponding to known specific single nucleotide polymorphisms - SNPs) in key oxidant enzymes, altering their activities (Harper and Saed, 2018).

In a more recent study, talcum powder increased mRNA levels of pro-oxidant enzymes in normal ovarian epithelial cells and ovarian cancer cell lines, while decreasing the mRNA levels of

antioxidant enzymes (Saed et al., 2017; Saed et al., 2018). A follow-up study reported in an abstract showed epithelial ovarian cancer cells treated with talc to demonstrate increased levels of CA-125 (Fletcher, 2018^b). CA-125 is a biomarker that has been found to be elevated in patients with ovarian cancer and is currently FDA approved for disease monitoring in patients with epithelial ovarian cancer, as well as those with BRCA mutations or who are in another in high-risk group.

D. Asbestos, Fibrous Talc, Heavy Metals and Fragrance Chemicals

In addition to the mineral talc, I have seen evidence that talcum powder products, including Johnson's Baby Powder and Shower to Shower, contain asbestos², and heavy metals³ such as chromium, cobalt, and nickel. A 2017 study by Longo and Rigler on historic samples of Johnson & Johnson baby powder ranging in production date over a span of many years showed over one-half (17 of 30) of Johnson's talcum powder product samples contained asbestos (Longo and Rigler, 2017). Talc containing asbestiform fibers (fibrous talc) was found in 15 of the 30 samples. A 2018 study by Longo and Rigler reported the presence of fibrous anthophyllite in products tested from 1978 as well as fibrous talc in both (Longo and Rigler, 2018). Additionally, I have reviewed the expert report of Drs. Longo and Rigler reporting that 37 of 56 historical talcum powder samples contained asbestos and 41 of the 42 samples tested contained fibrous talc⁴.

Asbestos has long been recognized as a well-known carcinogen and exposure can cause lung disease, mesothelioma, and cancers of the lung, larynx, and ovary (IARC 1987, 2012). It is established that asbestos exposure can result in macrophage activation, inflammation, generation of reactive oxygen and reactive nitrogen species, tissue injury, genotoxicity, and resistance to programmed cell death (Aust, 2011; Hein, 2007; IARC, 2012; Jaurand, 1997; Wang, 1987). One of the direct mechanisms is through interactions between internalized fibers and components of mitosis, resulting in chromosomal alterations and abnormalities (Hesterberg et al., 1986; Wang et al., 1987; Yegles et al., 1993). IARC has classified asbestos as a known human carcinogen (Group

² Ex. 28, Hopkins Dep. (Aug. 16 & 17, 2018; Oct. 17, 2018; and Nov. 5, 2018); Blount, 1991; Paoletti, 1984.

³ Ex. 47, Julie Pier Dep. (Sept. 12 & 13, 2018).

⁴ Expert Report of William E. Longo, PhD and Mark W. Rigler, PhD (Nov. 14, 2018).

1). Human tumors resulting from asbestos exposure can be characterized by genetic and chromosomal alterations that lead to the inactivation of tumor-suppressor genes (IARC, 2012).

Talc not containing asbestiform fibers has been found by IARC to be a Group 2b or “possible” carcinogen (IARC, 2010). IARC has determined that fibrous talc or talc containing asbestiform fibers (talc occurring in a fibrous habit) is a carcinogen to humans (IARC, 2012).

Chromium and nickel are classified by IARC as Group 1, “carcinogenic to humans” (IARC, 2012). Cobalt is classified as Group 2B, “possibly carcinogenic to humans” (IARC, 2006). IARC defines possibly carcinogenic as “a positive association has been observed between exposure to the agent and cancer for which a causal interpretation has been considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.” Established carcinogenic mechanisms of chromium include DNA damage, mutation, genomic instability, and cell transformation (IARC, 2009). Similar mechanisms result from nickel exposure (IARC, 2012). Cobalt exposure has been shown to cause increased production of reactive oxygen species and other inflammatory and proliferative changes (IARC, 2006).

I also reviewed Dr. Michael Crowley’s report discussing the numerous fragrance chemicals added to talcum powder products. I am in agreement with Dr. Crowley’s opinion that these chemicals contribute to the inflammatory properties, toxicity, and potential carcinogenicity of the products. The presence of these constituents as part of talcum powder products provides additional evidence of biological plausibility for talc and ovarian cancer.⁵

Carcinogenesis is a complex and dynamic process that occurs due to a combination of mutations, both genetic and acquired, in an individual along with other processes. Mutations arising from environmental sources have an additive, and possibly multiplicative effect toward ultimately causing carcinogenesis (Park, 2018; Vitonis, 2011; Wu, 2015). The presence of asbestos, nickel, and chromium, known carcinogens, in talcum powder products provides further support for the conclusion that talcum powder causes chronic inflammation.

⁵ Expert Report of Michael Crowley, PhD (Nov. 12, 2018).

Based on these observations and lines of evidence, it is my opinion that talcum powder causes inflammation which initiates a biological response that includes oxidative stress, cell proliferation, inhibition of apoptosis, and genetic mutations which result in cancer development and progression. This process explains the biologically plausible mechanism for talcum powder products causing ovarian cancer.

VII. Conclusion

Based on my background, training, education, and experience as a geneticist assessing and weighing the totality of scientific evidence, my opinions may be summarized as follows:

1. Genetic mutations can be inherited or acquired. Both types are associated with cancer, including ovarian cancer.
2. Talcum powder products cause chronic inflammation.
3. Talcum powder product-induced inflammation causes damage to the DNA, genetic mutation, genomic instability, and cell transformation.
4. The properties of talcum powder products as inflammatory agents and the role of inflammation in triggering oxidative stress, activating cytokines, cell proliferation, DNA damage, and genetic mutations (such as SNVs) provide a biologically plausible mechanism for the carcinogenicity of talcum powder products.
5. Internalization of asbestiform fibers (including fibrous talc), cause DNA damage which provides a biologically plausible mechanism for the carcinogenicity of talcum powder products.
6. The presence of an inherited gene mutation, such as *BRCA1* or *BRCA2*, indicates a woman has an increased risk of ovarian cancer, but does not necessarily mean she will develop ovarian cancer.
7. Women with inherited gene mutations, such as *BRCA*, are at least as susceptible to other carcinogens as women without inherited gene mutations.

I reserve the right to supplement, revise, or amend this report should additional materials, including testimony, become available.

Literature Cited

Adami, H.O., Hsieh, C.C., Lambe, M., Trichopoulos, D., Leon, D., Persson, I., Ekbom, A., and Janson, P.O. (1994). Parity, age at first childbirth, and risk of ovarian cancer. *Lancet* 344, 1250-1254.

Agic, A., Xu, H., Finas, D., Banz, C., Diedrich, K., and Hornung, D. (2006). Is endometriosis associated with systemic subclinical inflammation? *Gynecol Obstet Invest* 62, 139-147.

Aust, A.E., Cook, P.M., and Dodson, R.F. Morphological and chemical mechanisms of elongated mineral particle toxicities. *J Toxicol and Environ Health, Part B.* (2011) 14:40-75.

Balkwill, F., and Mantovani, A. (2001). Inflammation and cancer: back to Virchow? *Lancet* 357, 539-545.

Banerjee, S., and Kaye, S.B. (2013). New strategies in the treatment of ovarian cancer: current clinical perspectives and future potential. *Clin Cancer Res* 19, 961-968.

Barnes, D.R., and Antoniou, A.C. (2012). Unravelling modifiers of breast and ovarian cancer risk for BRCA1 and BRCA2 mutation carriers: update on genetic modifiers. *J Intern Med* 271, 331-343.

Belotte, J., Fletcher, N.M., Saed, M.G., Abusamaan, M.S., Dyson, G, Diamond, M.P., Saed, G.M. (2015) A single nucleotide polymorphism in catalase is strongly associated with ovarian cancer survival. *PLoS ONE* 10(8): e0135739. Doi: 10.1371/journal.pone.0135739.

Berek, J.S., Crum, C., and Friedlander, M. (2012). Cancer of the ovary, fallopian tube, and peritoneum. *Int J Gynaecol Obstet* 119 Suppl 2, S118-129.

Blount, A.M. (1991). Amphibole content of cosmetic and pharmaceutical talcs. *Environ Health Perspect* 94, 225-230.

Bodmer, M., Becker, C., Meier, C., Jick, S.S., and Meier, C.R. (2011). Use of metformin and the risk of ovarian cancer: a case-control analysis. *Gynecol Oncol* 123, 200-204.

Bonovas, S., Filioussi, K., and Sitaras, N.M. (2005). Do nonsteroidal anti-inflammatory drugs affect the risk of developing ovarian cancer? A meta-analysis. *Br J Clin Pharmacol* 60, 194-203.

Bowtell, D.D. (2010). The genesis and evolution of high-grade serous ovarian cancer. *Nat Rev Cancer* 10, 803-808.

Buz'Zard, Amber R., and Benjamin H. S. Lau. "Pycnogenol® Reduces Talc-Induced Neoplastic Transformation in Human Ovarian Cell Cultures." *Phytotherapy Research* 21, No. 6 (June 2007): 579–86.

Camargo, M.C., Stayner, L.T., Straif, K., Reina, M., Al-Alem, U., Demers, P.A., and Landrigan, P.J. (2011). Occupational exposure to asbestos and ovarian cancer: a meta-analysis. *Environ Health Perspect* 119, 1211-1217.

Casagrande, J.T., Louie, E.W., Pike, M.C., Roy, S., Ross, R.K., and Henderson, B.E. (1979). "Incessant ovulation" and ovarian cancer. *Lancet* 2, 170-173.

Catalani, S. (2009). [Lancet-Oncology--a summary of the review on IARC carcinogens: metallic elements, dusts and fibers]. *G Ital Med Lav Ergon* 31, 182-183.

Chan, J.K., Cheung, M.K., Husain, A., Teng, N.N., West, D., Whittemore, A.S., Berek, J.S., and Osann, K. (2006). Patterns and progress in ovarian cancer over 14 years. *Obstet Gynecol* 108, 521-528.

Charbonneau, B., Goode, E.L., Kalli, K.R., Knutson, K.L., and Derycke, M.S. (2013). The immune system in the pathogenesis of ovarian cancer. *Crit Rev Immunol* 33, 137-164.

Coussens, L.M., Tinkle, C.L., Hanahan, D., and Werb, Z. (2000). MMP-9 supplied by bone marrow-derived cells contributes to skin carcinogenesis. *Cell* 103, 481-490.

Coussens, L.M., and Werb, Z. (2002). Inflammation and cancer. *Nature* 420, 860-867.

Dvorak, H.F. (1986). Tumors: wounds that do not heal. Similarities between tumor stroma generation and wound healing. *N Engl J Med* 315, 1650-1659.

Fletcher, N.M., Belotte, J., Saed, M.G., Memaj, I., Diamond, M.P., Morris, R.T., Saed, G.M. Specific point mutations in key redox enzymes are associated with chemoresistance in epithelial ovarian cancer. *Free Radical Biology and Medicine* (2017) 102:122-132.

Fletcher^a, N.M., Memaj, I., and Saed, G.M. (2018). Talcum Powder Enhances Oxidative Stress in Ovarian Cancer Cells. Paper presented at: REPRODUCTIVE SCIENCES (SAGE PUBLICATIONS INC 2455 TELLER RD, THOUSAND OAKS, CA 91320 USA).

Fletcher^b, N.M., Saed, G.M. (2018). Talcum Powder enhances cancer antigen 125 levels in ovarian cancer cells and in normal ovarian epithelial cells. LB-044. Poster presented at: Society for Reproductive Investigation. 65th annual meeting. San Diego, CA.

Franklin, R.A., and Li, M.O. (2016). Ontogeny of Tumor-associated Macrophages and Its Implication in Cancer Regulation. *Trends Cancer* 2, 20-34.

Gates, M.A., Tworoger, S.S., Terry, K.L., Titus-Ernstoff, L., Rosner, B., De Vivo, I., Cramer, D.W., and Hankinson, S.E. (2008). Talc use, variants of the GSTM1, GSTT1, and NAT2 genes, and risk of epithelial ovarian cancer. *Cancer Epidemiol Biomarkers Prev* 17, 2436-2444.

Hamilton, T.C., Fox, H., Buckley, C.H., Henderson, W.J., and Griffiths, K. Effects of talc on the rat ovary. *Br. J. Exp. Path.* (1984) 65: 101-106.

Harper, A.K., Saed, G.M. Talc induces a pro-oxidant state in normal and ovarian cancer cells through gene point mutations in key redox enzymes. Accepted for presentation at SGO meeting 2019. [In Press].

Hein, M.J., Stayner, L.T., Lehman, E., Dement, J.M. Follow-up study of chrysotile textile workers: cohort mortality and exposure-response. *Occup Environ Med* (2007) 64:616-625.

Heller, D.S., Gordon, R.E., Westhoff, C., and Gerber, S. (1996). Asbestos exposure and ovarian fiber burden. *Am J Ind Med* 29, 435-439.

Hesterberg, T.W., Butterick, C.J., Oshimura, M., Brody, A.R., and Barrett, J.C. (1986). Role of phagocytosis in Syrian hamster cell transformation and cytogenetic effects induced by asbestos and short and long glass fibers. *Cancer Res* 46, 5795-5802.

International Agency for Research on Cancer (IARC), "Silica and Some Silicates", IARC Monograph No. 42 (1987).

International Agency for Research on Cancer (IARC), "Cobalt in Hard Metals and Cobalt Sulfate, Gallium Arsenide, Indium Phosphide and Vanadium Pentoxide," IARC Monograph No. 86 (2006).

International Agency for Research on Cancer (IARC), "Arsenic, Metals, Fibres, and Dusts," IARC Monograph No. 100C (2009).

International Agency for Research on Cancer (IARC), "Carbon Black, Titanium Dioxide, and Talc", IARC Monograph No. 93 (2010).

International Agency for Research on Cancer (IARC), "Arsenic, Metals, Fibres, and Dusts", IARC Monograph No. 100C (2012).

Irie, H., Banno, K., Yanokura, M., Iida, M., Adachi, M., Nakamura, K., Umene, K., Nogami, Y., Masuda, K., Kobayashi, Y., *et al.* (2016). Metformin: A candidate for the treatment of gynecological tumors based on drug repositioning. *Oncol Lett* 11, 1287-1293.

Jayson, G.C., Kohn, E.C., Kitchener, H.C., and Ledermann, J.A. (2014). Ovarian cancer. *Lancet* 384, 1376-1388.

Jaurand, M.C. Mechanisms of fiber-induced genotoxicity. *Environ Health Perspect* (1997) 105(Suppl 5):1073-1084.

Jia, D., Nagaoka, Y., Katsumata, M., and Orsulic, S. (2018). Inflammation is a key contributor to ovarian cancer cell seeding. *Sci Rep* 8, 12394.

Jordan, S.J., Cushing-Haugen, K.L., Wicklund, K.G., Doherty, J.A., and Rossing, M.A. (2012). Breast-feeding and risk of epithelial ovarian cancer. *Cancer Causes Control* 23, 919-927.

Keskin, N., Teksen, Y.A., Ongun, E.G., Ozay, Y., Saygili, H. Does long-term talc exposure have a carcinogenic effect on the female genital system of rats? An experimental pilot study. *Arch Gynecol Obstet.* (2009). 280:925-931.

Kisielewski, R., Tolwinska, A., Mazurek, A., and Laudanski, P. (2013). Inflammation and ovarian cancer--current views. *Ginek Pol* 84, 293-297.

Langseth, H., Johansen, B.V., Nesland, J.M., and Kjaerheim, K. (2007). Asbestos fibers in ovarian tissue from Norwegian pulp and paper workers. *Int J Gynecol Cancer* 17, 44-49.

Levanon, K., Crum, C., Drapkin, R. New insights into the pathogenesis of serous ovarian cancer and its clinical impact. *J Clin Oncol.* (2008). Nov 10;26(32):5284-93.

Li, D. (2011). Metformin as an antitumor agent in cancer prevention and treatment. *J Diabetes* 3, 320-327.

Lin, H.W., Tu, Y.Y., Lin, S.Y., Su, W.J., Lin, W.L., Lin, W.Z., Wu, S.C., and Lai, Y.L. (2011). Risk of ovarian cancer in women with pelvic inflammatory disease: a population-based study. *Lancet Oncol* 12, 900-904.

Liu, Y., and Cao, X. (2015). The origin and function of tumor-associated macrophages. *Cell Mol Immunol* 12, 1-4.

Longo, W., and Rigler, M. (2017). Analysis of Johnson & Johnson Baby Powder & Valiant Shower to Shower Talc Products for Amphibole (Tremolite) Asbestos (Materials Analytical Services, LLC).

Longo, W., and Rigler, M. (2018). TEM Analysis of Historical 1978 Johnson's Baby Powder Sample for Amphibole Asbestos (Materials Analytical Services, LLC).

Mabuchi, S., Kawase, C., Altomare, D.A., Morishige, K., Sawada, K., Hayashi, M., Tsujimoto, M., Yamoto, M., Klein-Szanto, A.J., Schilder, R.J., *et al.* (2009). mTOR is a promising therapeutic target both in cisplatin-sensitive and cisplatin-resistant clear cell carcinoma of the ovary. *Clin Cancer Res* 15, 5404-5413.

Maccio, A., and Madeddu, C. (2012). Inflammation and ovarian cancer. *Cytokine* 58, 133-147.

Mahdavi, A., Pejovic, T., and Nezhat, F. (2006). Induction of ovulation and ovarian cancer: a critical review of the literature. *Fertil Steril* 85, 819-826.

Mantovani, A., Bottazzi, B., Colotta, F., Sozzani, S., and Ruco, L. (1992a). The origin and function of tumor-associated macrophages. *Immunol Today* 13, 265-270.

Mantovani, A., Bussolino, F., and Dejana, E. (1992b). Cytokine regulation of endothelial cell function. *FASEB J* 6, 2591-2599.

Mantovani, A., Bussolino, F., and Introna, M. (1997). Cytokine regulation of endothelial cell function: from molecular level to the bedside. *Immunol Today* 18, 231-240.

Merritt, M.A., Green, A.C., Nagle, C.M., Webb, P.M., Australian Cancer, S., and Australian Ovarian Cancer Study, G. (2008). Talcum powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer. *Int J Cancer* 122, 170-176.

Mills, P.K., Riordan, D.G., Cress, R.D., and Young, H.A. (2004). Perineal talc exposure and epithelial ovarian cancer risk in the Central Valley of California. *Int J Cancer* 112, 458-464.

Modan, B., Hartge, P., Hirsh-Yechezkel, G., Chetrit, A., Lubin, F., Beller, U., Ben-Baruch, G., Fishman, A., Menczer, J., Struewing, J.P., *et al.* (2001). Parity, oral contraceptives, and the risk of ovarian cancer among carriers and noncarriers of a BRCA1 or BRCA2 mutation. *N Engl J Med* 345, 235-240.

Mor, G., Yin, G., Chefetz, I., Yang, Y., and Alvero, A. (2011). Ovarian cancer stem cells and inflammation. *Cancer Biol Ther* 11, 708-713.

Narod, S.A., Risch, H., Moslehi, R., Dorum, A., Neuhausen, S., Olsson, H., Provencher, D., Radice, P., Evans, G., Bishop, S., *et al.* (1998). Oral contraceptives and the risk of hereditary ovarian cancer. Hereditary Ovarian Cancer Clinical Study Group. *N Engl J Med* 339, 424-428.

National Toxicology Program. Toxicology and carcinogenesis studies of talc (CAS No. 14807-96-6) in F344/N rats and B6C3F₁ mice (Inhalation studies); 1993. Report No. NTP TR 421; NIH Publication No. 93-3152.

Ness, Roberta B., Jeane Ann Grisso, Carrie Cottreau, Jennifer Klapper, Ron Vergona, James E. Wheeler, Mark Morgan, and James J. Schlesselman. "Factors Related to Inflammation of the Ovarian Epithelium and Risk of Ovarian Cancer." *Epidemiology* 11, No. 2 (2000): 111-17.

Nunes, S.C., and Serpa, J. (2018). Glutathione in Ovarian Cancer: A Double-Edged Sword. *Int J Mol Sci* 19.

Paluch-Shimon, S., Cardoso, F., Sessa, C., Balmana, J., Cardoso, M.J., Gilbert, F., Senkus, E., and Committee, E.G. (2016). Prevention and screening in BRCA mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO Clinical Practice Guidelines for cancer prevention and screening. *Ann Oncol* 27, v103-v110.

Paoletti, L., Caiazza, S., Donelli, G., and Pocchiari, F. (1984). Evaluation by electron microscopy techniques of asbestos contamination in industrial, cosmetic, and pharmaceutical talcs. *Regul Toxicol Pharmacol* 4, 222-235.

Pardoll, D.M. (2002). Spinning molecular immunology into successful immunotherapy. *Nat Rev Immunol* 2, 227-238.

Park, H.K., Schildkraut, J.M., Alberg, A.J., Bandera, E.V., Barnholtz-Sloan, J.S., Bondy, M., Crankshaw, S., Funkhouser, E., Moorman, P.G., Peters, E.S., *et al.* (2018). Benign gynecologic conditions are associated with ovarian cancer risk in African-American women: a case-control study. *Cancer Causes Control* 29, 1081-1091.

Pejovic, T., and Nezhat, F. (2011). Missing link: inflammation and ovarian cancer. *Lancet Oncol* 12, 833-834.

Penninkilampi, Ross and Guy D. Eslick. "Perineal Talc Use and Ovarian Cancer: A Systematic Review and Meta-Analysis." *Epidemiology* 29, No. 1 (January 2018): 41-49.

Ramus, S.J., Vierkant, R.A., Johnatty, S.E., Pike, M.C., Van Den Berg, D.J., Wu, A.H., Pearce, C.L., Menon, U., Gentry-Maharaj, A., Gayther, S.A., *et al.* (2008). Consortium analysis of 7 candidate SNPs for ovarian cancer. *Int J Cancer* 123, 380-388.

Rebbeck, T.R., Mitra, N, Wan, F., Sinilnikova, O.M., Healey, S., McGuffog, L., Mazoyer, S., Chenevix-Trench, G., Easton, D.F., Antoniou, A.C., Nathanson, K.L., the CIMBA Consortium. Association of type and location of BRCA1 and BRCA2 mutations with risk of breast and ovarian cancer. *JAMA.* (2015). April 7; 313(13):1347-1361.

Reid, B.M., Permuth, J.B., Sellers, T.A. Epidemiology of ovarian cancer: a review. *Cancer Med Biol.* (February 2017) Vol 14, No 1.

Rosenblatt, K.A., Weiss, N.S., Cushing-Haugen, K.L., Wicklund, K.G., and Rossing, M.A. (2011). Genital powder exposure and the risk of epithelial ovarian cancer. *Cancer Causes Control* 22, 737-742.

Saed, G.M., Diamond, M.P., and Fletcher, N.M. (2017). Updates of the role of oxidative stress in the pathogenesis of ovarian cancer. *Gynecol Oncol* 145, 595-602.

Saed, G.M., Morris, R.T., and Fletcher, N.M. (2018). New Insights into the Pathogenesis of Ovarian Cancer: Oxidative Stress. In *Ovarian Cancer-From Pathogenesis to Treatment* (IntechOpen).

Sellers, T.A., Huang, Y., Cunningham, J., Goode, E.L., Sutphen, R., Vierkant, R.A., Kelemen, L.E., Fredericksen, Z.S., Liebow, M., Pankratz, V.S., *et al.* (2008). Association of single nucleotide polymorphisms in glycosylation genes with risk of epithelial ovarian cancer. *Cancer Epidemiol Biomarkers Prev* 17, 397-404.

Shan, W., and Liu, J. (2009). Inflammation: a hidden path to breaking the spell of ovarian cancer. *Cell Cycle* 8, 3107-3111.

Shen, H., Fridley, B.L., Song, H., Lawrenson, K., Cunningham, J.M., Ramus, S.J., Cicek, M.S., Tyrer, J., Stram, D., Larson, M.C., *et al.* (2013). Epigenetic analysis leads to identification of HNF1B as a subtype-specific susceptibility gene for ovarian cancer. *Nat Commun* 4, 1628.

Shukla, A., MacPherson, M.B., Hillegass, J., Ramos-Nino, M.E., Alexeeva, V., Vacek, P.M., Bond, J.P., Pass, H.I., Steele, C., Mossman, B.T. Alterations in gene expression in human mesothelial cells correlate with mineral pathogenicity. *Am J Respir Cell Mol Biol.* (2009). 41:114-123.

Siegel, R.L., Miller, K.D., and Jemal, A. (2015). Cancer statistics, 2015. *CA Cancer J Clin* 65, 5-29.

Titus-Ernstoff, L., Perez, K., Cramer, D.W., Harlow, B.L., Baron, J.A., and Greenberg, E.R. (2001). Menstrual and reproductive factors in relation to ovarian cancer risk. *Br J Cancer* 84, 714-721.

Torre, L.A., Bray, F., Siegel, R.L., Ferlay, J., Lortet-Tieulent, J., and Jemal, A. (2015). Global cancer statistics, 2012. *CA Cancer J Clin* 65, 87-108.

Trabert, B., Ness, R.B., Lo-Ciganic, W.H., Murphy, M.A., Goode, E.L., Poole, E.M., Brinton, L.A., Webb, P.M., Nagle, C.M., Jordan, S.J., *et al.* (2014). Aspirin, nonaspirin nonsteroidal anti-inflammatory drug, and acetaminophen use and risk of invasive epithelial ovarian cancer: a pooled analysis in the Ovarian Cancer Association Consortium. *J Natl Cancer Inst* 106, djt431.

Vitonis, A.F., Titus-Ernstoff, L., and Cramer, D.W. (2011). Assessing ovarian cancer risk when considering elective oophorectomy at the time of hysterectomy. *Obstet Gynecol* 117, 1042-1050.

Wang, N.S., Jaurand, M.C., Magne, L., Kheuang, L., Pinchon, M.C., and Bignon, J. (1987). The interactions between asbestos fibers and metaphase chromosomes of rat pleural mesothelial cells in culture. A scanning and transmission electron microscopic study. *Am J Pathol* 126, 343-349.

Wehner, A.P. (1994). Biological effects of cosmetic talc. *Food Chem Toxicol* 32, 1173-1184.

Wu, A.H., Pearce, C.L., Tseng, C.C., and Pike, M.C. (2015). African Americans and Hispanics Remain at Lower Risk of Ovarian Cancer Than Non-Hispanic Whites after Considering Nongenetic Risk Factors and Oophorectomy Rates. *Cancer Epidemiol Biomarkers Prev* 24, 1094-1100.

Wu, A.H., Pearce, C.L., Tseng, C.C., Templeman, C., and Pike, M.C. (2009). Markers of inflammation and risk of ovarian cancer in Los Angeles County. *Int J Cancer* 124, 1409-1415.

Yegles, M., Saint-Etienne, L., Renier, A., Janson, X., and Jaurand, M.C. (1993). Induction of metaphase and anaphase/telophase abnormalities by asbestos fibers in rat pleural mesothelial cells in vitro. *Am J Respir Cell Mol Biol* 9, 186-191.

Exhibit A

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Curriculum Vitae

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Personal Statement

My group has been utilizing high performance genotyping and sequencing technologies for the past 15 years supporting a vast diversity of projects from plant and animal phylogenetic studies to translational and clinical based projects. We have several publications detailing our successes using variety of genomic technologies as well as in the field of bioinformatics research. As a post-doctoral fellow at Emory University I developed the first microarray designed to interrogate mitochondrial gene function. Upon joining the faculty at Vanderbilt University, I was responsible for the founding and development of the Vanderbilt Microarray Shared Resource (VMSR). From 2000 to 2009, the VMSR became an internationally recognized facility supporting a wide variety of genomic technologies from SNP profiling to gene expression analysis to next-generation sequencing. I joined the faculty of the HudsonAlpha Institute for Biotechnology in 2009 to develop the Genomic Services Laboratory (GSL). Since 2009 the GSL has supported more than 1,000 principle investigators from around the world, allowing me to collaborate and participate in a broad range of genomics projects with a particular focus on applying a diversity of genomic methods to understand complex conditions. We have had a particular focus on childhood and adult cancer as well as rare disease and degenerative diseases. Together, these efforts have resulted in more than 140 peer-reviewed publications of which I am an author or co-author. More than 150 additional publications that have included data from our laboratory as a service provider have also been published since 2009. Many of these publications involve translational research or describe the genetic underpinnings of rare or complex human disease. The diversity of projects and investigators we have worked with over the last 15 years have provided a dynamic and amazing experience to evolve our own research and technology development efforts.

Contributions to Science

The following five sections provide highlights to areas where my work has contributed to areas of science. Example publications are provided with each section and a full bibliography is provided at the end of the CV.

1. My scientific career has been a somewhat atypical in that I have spent the last 15 years focusing on the development and application of genomic and bioinformatic technologies and methods to support scientific investigation in a number of areas. While there have been substantial areas of focus, my laboratory does not operate under a single or specific biological area or hypothesis. Instead, we examine ways to improve the resolution and quality of results to answer complex questions, regardless of biological relationship. The publications below are examples of contributions to technical projects or large consortium projects with goals in the evaluation or improvement of techniques or technologies.
 - a. Statnikov A, Aliferis, C, Tsamardinos, I, Hardin, D, and Levy, S. A comprehensive evaluation of multicategory classification methods for microarray gene expression cancer diagnosis. **Bioinformatics**, 2005. 21(5), p. 631-643. PMID:15374862.

- b. The MicroArray Quality Control Consortium. The MicroArray Quality Control (MAQC) project shows inter- and intraplatform reproducibility of gene expression measurements. **Nature Biotechnology**, 2006. 24(9), p. 1151-1161. PMID:16964229.
 - c. The ENCODE Project Consortium. An integrated encyclopedia of DNA elements in the human genome. **Nature**. 2012. 489, 57-74. PMID: 22955616 PMCID: PMC3439153
 - d. The Sequence Quality Control (SEQC) Consortium. A comprehensive assessment of RNA-seq accuracy, reproducibility and information content by the Sequence Quality Control consortium. **Nature Biotechnology**. 2014. 32 (9), 915-925. PMID:25150835; PMCID:4167418.
2. One area of early focus of my career was the development and analysis of mouse models for mitochondrial disease, including the knock out of the Adenine Nucleotide Translocase 2 (Ant2) gene leading to a more complete understanding of the permeability transition. This work also discovered methods to alter the mitochondrial DNA in stem cells and supported the first mitochondrial DNA transfers by stem cells.
- a. Levy SE, Waymire, KG, Kim, YL, MacGregor, GR, and Wallace, DC, Transfer of chloramphenicol-resistant mitochondrial DNA into the chimeric mouse. **Transgenic Research**. 1999. 8(2), p. 137-145. PMID:10481313.
 - b. Sligh JE, Levy SE, Waymire KG, Allard P, Dillehay DL, Nusinowitz S, Heckenlively JR, MacGregor GR, and Wallace DC. Maternal germ-line transmission of mutant mtDNAs from embryonic stem cell-derived chimeric mice. **Proc. of the Nat. Acad. of Sciences USA**. 2000. 97(26), p. 14461-14466. PMID:11106380; PMCID:18941.
 - c. Kokoszka JE, Waymire, KG, Levy, SE, Sligh, JE, Cal, JY, Jones, DP, MacGregor, GR, and Wallace, DC, The ADP/ATP translocator is not essential for the mitochondrial permeability transition pore. **Nature**, 2004. 427(6973),p. 461-465. PMID:14749836.
 - d. Picard M, Zhang J, Hanecock S, Derbeneva O, Golhar R, Golik P, O'Hearn S, Levy SE, Potluri P, Lvova M, Davila A, Lin CS, Perin JC, Rappaport EF, Hakonarson H, Trounce I, Procaccio V, and Wallace DC. Progressive increase in mtDNA 3243A>G heteroplasmy results in abrupt transcriptional remodeling. **Proc. of the Nat. Acad. of Sciences USA**. 2014. 111(38), E4033-E4042. PMID:25192935; PMCID:4183335.
3. A long-standing area of research interest is the genomic analysis of cancer, both childhood and adult. These efforts have included population-based studies and more directed research in specific cancer biology. These efforts have examined many cancer types including breast, lung, colon, and myeloid cancer.
- a. Smith JJ, Deane, NG, Wu, F, Merchant, NB, Zhang, B, Jiang, A, Lu, P, Johnson, JC, Schmidt, C, Edwards, CM, Eschrich, S, Kis, C, Levy, S, Washington, MK, Heslin, MJ, Coffey, RJ, Yeatman, TJ, Shyr, Y, and Beauchamp, RD, Experimentally Derived Metastasis Gene Expression Profile Predicts Recurrence and Death in Patients With Colon Cancer. **Gastroenterology**, 2009. PMID: 19914252 PMCID: PMC3388775.
 - b. Powell AE, Wang Y, Li Y, Poulin EJ, Means AL, Washington MK, Higginbotham JN, Juchheim A, Prasad N, Levy SE, Guo Y, Shyr Y, Aronow BJ, Haigis KM, Franklin JL, and Coffey RJ. Lrig1, a pan-ErbB negative regulator, marks intestinal stem cells and acts as a tumor suppressor. **Cell**. 2012. 149(1), 146-158. PMID: 22464327 PMCID: PMC3563328.
 - c. McDaniel JM, Varley KE, Gertz J, Savic DS, Roberts BS, Bailey SK, Shevde LA, Ramaker RC, Lasseigne BN, Kirby MK, Newberry KM, Partridge EC, Jones AL, Boone B, Levy SE, Oliver PG, Sexton KC, Grizzle WE, Forero A, Buchsbaum DJ, Cooper SJ, Myers RM. Genomic regulation of invasion by STAT3 in triple negative breast cancer. **Oncotarget**. 2017;8(5):8226-38. doi: 10.18632/oncotarget.14153. PubMed PMID: 28030809; PMCID: PMC5352396.

- d. McKinney M, Moffitt AB, Gaulard P, Travert M, De Leval L, Nicolae A, Raffeld M, Jaffe ES, Pittaluga S, Xi L, Heavican T, Iqbal J, Belhadj K, Delfau-Larue MH, Fatacciolli V, Czader MB, Lossos IS, Chapman-Fredricks JR, Richards KL, Fedoriw Y, Ondrejka SL, Hsi ED, Low L, Weisenburger D, Chan WC, Mehta-Shah N, Horwitz S, Bernal-Mizrachi L, Flowers CR, Beaven AW, Parihar M, Baseggio L, Parrens M, Moreau A, Sujobert P, Pilichowska M, Evens AM, Chadburn A, Au-Yeung RK, Srivastava G, Choi WW, Goodlad JR, Aurer I, Basic-Kinda S, Gascoyne RD, Davis NS, Li G, Zhang J, Rajagopalan D, Reddy A, Love C, Levy S, Zhuang Y, Datta J, Dunson DB, Dave SS. The Genetic Basis of Hepatosplenic T-cell Lymphoma. **Cancer Discov.** 2017;7(4):369-79. doi: 10.1158/2159-8290.CD-16-0330. PubMed PMID: 28122867; PMCID: PMC5402251.
4. My laboratory has had the opportunity to collaborate with a number of outstanding investigators in the genetics analysis of complex neurological conditions, including autism, schizophrenia and bipolar disorders as well as ALS. We contributed significantly to the discovery of the association of de-novo rather than Mendelian mutations in these conditions, particularly in schizophrenia.
 - a. Xu B, Roos JL, Dexheimer P, Boone B, Plummer B, Levy S, Gogos JA, Karayiorgou M. Exome sequencing supports a de novo mutational paradigm for schizophrenia. **Nature Genetics.** 2011. 43(9), 864-868. PMID: 21822266. PMCID: PMC3196550.
 - b. Neale BM, Kou Y, Liu L, Ma'ayan A, Samocha KE, Sabo A, Lin CF, Stevens C, Wang LS, Makarov V, Polak P, Yoon S, Maguire J, Crawford EL, Campbell NG, Geller ET, Valladares O, Shafer C, Liu H, Zhao T, Cai G, Lihm J, Dannenfelser R, Jabado O, Peralta Z, Nagaswamy U, Reid JG, Newsham I, Wu Y, Lewis L, Han Y, Muzny D, Voight BF, Lim E, Rossin E, Kirby A, Flannick J, Fromer M, Shakir K, Fennell T, Garimella K, Boyko C, Gabriel S, dePristo M, Wimbish JR, Boone BE, Levy SE, Betancur C, Sunyaev S, Boerwinkle E, Buxbaum JD, Cook EH, Devlin B, Gibbs R, Roeder K, Schellenberg GD, Sutcliffe JS, and Daly MJ. Patterns and rates of exonic de novo mutations in autism spectrum disorders. **Nature.** 2012. 485(7397), 242-245. PMID: 22495311 PMCID:PMC3613847.
 - c. Xu B, Ionita-Laza I, Roos JL, Boone B, Woodrick S, Sun Y, Levy S, Gogos JA, and Karayiorgou M. De novo gene mutations highlight patterns of genetic and neural complexity in schizophrenia. **Nature Genetics.** 2012. 44(12), 1365-1369. PMID: 23042115 PMCID: PMC3556813.
 - d. Cirulli, ET, Lasseigne, BN, Petrovski, S, Sapp, PC, Dion, PA, Leblond, CS, Couthouis, J, Lu, Y-F, Wang, Q, Krueger, BJ, Ren, Z, Keebler, J, Han, Y, Levy, SE, Boone, BE, Wimbish, JR, Waite, LL, Jones, AL, Carulli, JP, Day-Williams, AG, Staropoli, JF, Xin, WW, Chesi, A, Raphael, AR, McKenna-Yasek, D, Cady, J, Vianney de Jong, JMB, Kenna, KP, Smith, BN, Topp, S, Miller, J, Gkazi, A, Consortium, FS, Al-Chalabi, A, van den Berg, LH, Veldink, J, Silani, V, Ticozzi, N, Shaw, CE, Baloh, RH, Appel, S, Simpson, E, Lagier-Tourenne, C, Pulst, SM, Gibson, S, Trojanowski, JQ, Elman, L, McCluskey, L, Grossman, M, Shneider, NA, Chung, WK, Ravits, JM, Glass, JD, Sims, KB, Van Deerlin, VM, Maniatis, T, Hayes, SD, Ordureau, A, Swarup, S, Landers, J, Baas, F, Allen, AS, Bedlack, RS, Harper, JW, Gitler, AD, Rouleau, GA, Brown, R, Harms, MB, Cooper, GM, Harris, T, Myers, RM, Goldstein, DB. Exome sequencing in amyotrophic lateral sclerosis identifies risk genes and pathways. **Science.** 2015. Feb 19. pii: aaa3650. [Epub ahead of print] PubMed PMID: 25700176.
 5. My laboratory has played a significant role in the discovery of the causative mutations of a number of rare but significant human diseases, particularly in the field of pediatric nephrology in collaboration with Friedhelm Hildebrandt at Harvard University. These studies applied genomic technologies to better characterize and in some cases diagnose or discover the causative mutation for severe phenotypes or disease.
 - a. Otto EA, Hurd TW, Airik R, Chaki M, Zhou W, Stoetzel C, Patil SB, Levy S, Ghosh AK, Murga-Zamalloa CA, van Reeuwijk J, Letteboer SJF, Sang L, Giles RH, Liu Q, Coene KLM, Estrada-

- Cuzcano A, Collin RWJ, McLaughlin HM, Held S, Kasanuki JM, Ramaswami G, Conte J, Lopez I, Washburn J, MacDonald J, Hu, J, Yamashita Y, Maher ER, Guay-Woodford L, Neumann HPH, Obermuller H, Koenekoop RK, Bergmann C, Bei X, Lewis RA, Katsanis N, Lopes V, Williams DS, Lyons RH, Dang CV, Brito DA, Dias MB, Zhang X, Nurnberg G, Nurnberg P, Pierce E, Jackson P, Antignac C, Saunier S, Roepman R, Dollfus H, Khanna H, and Hildebrandt F. Candidate exome capture identifies mutation of SDCCAG8 as the cause of a retinal-renal ciliopathy. **Nature Genetics**. 2010. 42(10), 840-850 PMID: 20835237 PMCID: PMC2947620.
- b. Rademakers R, Baker M, Nicholson AM, Rutherford NJ, Finch N, Soto-Ortolaza A, Lash J, Wider C, Wojtas A, DeJesus-Hernandez M, Adamson J, Kouri N, Sundal C, Shuster EA, Aasly J, MacKenzie J, Roeber S, Kretzschmar HA, Boeve BF, Knopman DS, Petersen RC, Cairns NJ, Ghetti B, Spina S, Garbern J, Tselis AC, Uitti R, Das P, Van Gerpen JA, Meschia JF, Levy S, Broderick DF, Graff-Radford N, Ross OA, Miller BB, Swerdlow RH, Dickson DW, Wszolek ZK. Mutations in the colony stimulating factor 1 receptor (CSF1R) cause hereditary diffuse leukoencephalopathy with spheroids. **Nature Genetics**. 2011. 44(2), 200-205. PMID: 22197934 PMCID: PMC3267847.
- c. Fiskerstrand T, Arshad N, Haukanes BI, Tronstad RR, Pham KDC, Johansson S, Håvik B, Tønder SL, Levy SE, Brackman D, Boman H, Biswas KH, Apold J, Hovdenak N, Visweswariah SS, and Knappskog PM. Familial Diarrhea Syndrome Caused by an Activating GUCY2C Mutation. **New England Journal of Medicine**. 2012. 366(17), 1586-1595. PMID: 22436048.
- d. Carlson J, Scott LJ, Locke AE, Flickinger M, Levy S, Myers RM, Boehnke M, Kang HM, Li JZ, Zöllner S. Extremely rare variants reveal patterns of germline mutation rate heterogeneity in humans. **bioRxiv**. 2017:108290.
- e. Chao HT, Davids M, Burke E, Pappas JG, Rosenfeld JA, McCarty AJ, Davis T, Wolfe L, Toro C, Tifft C, Xia F, Stong N, Johnson TK, Warr CG, Undiagnosed Diseases N, Yamamoto S, Adams DR, Markello TC, Gahl WA, Bellen HJ, Wangler MF, Malicdan MC. A Syndromic Neurodevelopmental Disorder Caused by De Novo Variants in EBF3. **Am J Hum Genet**. 2017;100(1):128-37. doi: 10.1016/j.ajhg.2016.11.018. PubMed PMID: 28017372; PMCID: PMC5223093.

Education

College

University of New Hampshire: BS, 1994 (Biochemistry, Microbiology)
GPA 3.37
Honors Graduate, Dean's list.

Graduate School

Emory University: PhD, 2000, (Biochemistry)
GPA 3.75
Thesis title: "Genetic Alteration of the Mouse Mitochondrial Genome and Effects on Gene Expression."
Thesis advisor: Professor Douglas C. Wallace

Post-Graduate Training

Emory University, Douglas C. Wallace, March 2000-July 2000

Academic Appointments

Research Assistant Professor, Department of Molecular Physiology and Biophysics,
Vanderbilt University Medical Center, Nashville, TN, July 2000-June 2003

Adjunct Faculty, Graduate training program, Department of Biomedical Informatics,
Vanderbilt University Medical Center, Nashville, TN, January 2001-June 2003

Director, Vanderbilt Microarray Shared Resource, Vanderbilt University Medical Center,
Nashville, TN, July 2000-August 2009

Assistant Professor, Department of Biomedical Informatics, Vanderbilt University Medical
Center, Nashville, TN, July 2003-August 2009. (*Primary Appointment*)

Assistant Professor, Department of Molecular Physiology and Biophysics, Vanderbilt
University Medical Center, Nashville, TN, July 2003-August 2009 (*Secondary Appointment*)

Adjunct Associate Professor, Department of Biomedical Informatics, Vanderbilt University
Medical Center, Nashville, TN, August 2009-Present

Adjunct Associate Professor, Department of Epidemiology, University of Alabama-
Birmingham, Birmingham, AL October 2010-Present.

Adjunct Assistant Professor, Department of Genetics, University of Alabama-Birmingham,
Birmingham, AL October 2010-Present.

Adjunct Associate Professor, Department of Biological Sciences, University of Alabama-
Huntsville, Huntsville, AL January 2014-Present.

Faculty Investigator, HudsonAlpha Institute for Biotechnology, Huntsville, AL, August 2009-
Present

Executive Director, HudsonAlpha Clinical Services Laboratory, LLC, Huntsville, AL, December
2014-Present

Professional Organizations

American Medical Informatics Association, Co-chair, Genomics Working Group (2006-2007)
Association of Biomedical Resource Facilities
American Association for the Advancement of Science
American Association for Cancer Research
American Society for Human Genetics

Professional Activities

Intramural-University

Vision 2020 Personalized Medicine Committee-Task Force 3 (2009)

Intramural-Departmental

Department of Biomedical Informatics Academic Progress Committee (2005-2007)
Department of Biomedical Informatics Curriculum Committee (2007-2009)

Intramural-Center Affiliations

Vanderbilt-Ingram Cancer Center, Associate Member (2000-2009)
Vanderbilt Diabetes Research and Training Center, Member (2000-2009)

Vanderbilt Digestive Disease Research Center, Member (2003-2009)
Vanderbilt Institute of Chemical Biology, Member (2004-2009)

Extramural-Journal Review

- Reviewer- Arteriosclerosis, Thrombosis and Vascular Biology (2001-present)
- Reviewer-Bioinformatics (2001-present)
- Reviewer-Journal of Biological Chemistry (2002-present)
- Reviewer-Neuropsychopharmacology (2003-present)
- Reviewer-Kidney International (2003-present)
- Reviewer-Circulation Research (2003-present)
- Reviewer-Proceedings of the National Academy of Sciences (2004-present)
- Reviewer-Mitochondrion (2004-present)
- Reviewer-Molecular Nutrition and Food Research (2005-present)
- Reviewer-Pattern Recognition Letters (2006-present)
- Reviewer-PLOS-Genetics (2006-present)
- Reviewer-Physiological Genomics (2008-present)
- Reviewer-Genome Biology (2008-present)

Extramural-Editorial

- Member, Editorial Board- Journal of the American Informatics Association (2005-2007)

Extramural-Grant Study Section

- Reviewer- Alzheimer's Association (2002-present).
- NIDDK study section ZDK1 GRB-6 "Digestive Disease Research Development Centers" December 2002.
- NIDDK study section ZDK1 GRB-6 "Digestive Disease Research Development Centers" April 2004.
- NCI study section ZCA1 SRRB-C "Innovative Technologies for the Detection of Cancer" July 2004.
- NLM special study section-P41 Biomedical Informatics Resource Grants, April 2005.
- NLM special emphasis panel ZLM1 HS RO1, July 2005
- NIH CSR shared equipment study section ZRG1 GGG-T (30, 31), November 2005.
- DOD Ovarian Cancer Review Panel OC-2, August 2006
- NIH Special Emphasis Panel ZRG1 GGG-T Genomics and Genetics Shared Instrumentation, October 2006.
- NCI study section ZCA1 SRRB-U Development of Advanced Genomic Characterization Technologies, November 2006.
- NIDDK DK-06-017 "Silvio O. Conte Digestive Diseases Research Core Centers P30", June 2007.
- NIH Special Emphasis Panel ZRG1 GGG-A (30) - S10s genomics and proteomics shared instrumentation, July 2007.
- NIH Special Emphasis Panel ZRG1 GGG-B (30) - S10s genomics and proteomics shared instrumentation, September 2008.
- NIAAA Special Review Panel ZAA1-GG-01, November 2008
- NIH Special Emphasis Panel ZRG1 GGG-A (30) – Genes Genomes and Genetics instrumentation, October 2010.
- NIH Study Section 2011/05 GHD-Genetics of Health and Disease Study Section, February 2011.
- NIGRI Study Section 2012/05 ZHG1 HGR-P (M1) 1-H3 AFRICA Initiative, March 2012.

Extramural-Other Review

- Reviewer, American Association for the Advancement of Science Research Competitive Service-*Microarray Facilities for the Vermont Genetics Network*. April 2002.
- Reviewer, American Association for the Advancement of Science Research Competitive Service-*External Review of the Michigan Core Technology Alliance*. April 2003.
- Reviewer, American Association for the Advancement of Science Research Competitive Service-*External Review of the Michigan Core Technology Alliance*. April 2004.
- Reviewer, American Association for the Advancement of Science Research Competitive Service-*External Review of the Rhode Island EPScOR*. January 2007.
- Reviewer, American Association for the Advancement of Science Research Competitive Service-*External Review of the Rhode Island EPScOR*. March 2008.
- Reviewer, American Association for the Advancement of Science Research Competitive Service- *Review of Washington State Life Sciences Discovery Fund* June 2008.
- Reviewer, American Association for the Advancement of Science Research Competitive Service- *Review of Missouri Life Sciences Research Board* October 2008
- Reviewer, American Association for the Advancement of Science Research Competitive Service-*External Review of the Rhode Island EPScOR*. June 2009.
- Reviewer, American Association for the Advancement of Science Research Competitive Service-*External Review of the Rhode Island EPScOR*. May 2010.
- Reviewer, American Association for the Advancement of Science Research Competitive Service-*External Review of the Rhode Island EPScOR*. September 2011.

Extramural-Advisory

- Member, Scientific Advisory Board, NuGen Technologies, Inc, San Carlos, CA, October 2003-December 2010.
- Member, Scientific Advisory Board, Genome Quebec Innovation Centre, Montreal, Quebec, 2008-2011.
- Member, Scientific Advisory Board, Genomic Explorations Inc, Memphis, TN, 2006-present.
- Member, Scientific Advisory Board, Rubicon Genomics, Ann Arbor, MI 2013-present.
- Chairman, Scientific Advisory Board, RainDance Technologies (BioRad), Billerica, MA 2015-present.

Honors and Awards

- Scholar Athlete, University of New Hampshire, 1993-1994.
- Dean's list, University of New Hampshire, 1992-1994.
- Career Development Award, SPORE in Gastrointestinal Cancer 2004-2005
- Co-Chair, Genomics Working Group of the American Medical Informatics Association 2006-2007.

Teaching Activities

Graduate School Courses as Course Director

BMIF 310-Foundations of Bioinformatics and Computational Biology, 28 lectures, Spring 2004
BMIF 311-Introduction to Systems Biology, 28 lectures, Spring 2009. *This course was a newly developed course for 2009.*

Graduate School Courses as Lecturer

MPB 322-Regulation of Gene Expression, 3 lectures, Spring 2002
MPB 322-Regulation of Gene Expression, 2 lectures, Spring 2003
MPB 322-Regulation of Gene Expression, 3 lectures, Spring 2004

IGP 301-Methodology, 1 lecture, Fall 2004
IGP 301-Methodology, 1 lecture, Fall 2005
IGP 301-Methodology, 1 lecture, Fall 2006
MIM 351-Functional Genomics and Proteomics, 2 lectures, Spring 2006
BMIF 310-Foundations of Bioinformatics and Computational Biology, 7 lectures, Fall 2007
BMIF 310-Foundations of Bioinformatics and Computational Biology, 7 lectures, Fall 2008
BMIF 310-Foundations of Bioinformatics and Computational Biology, 4 lectures, Fall 2009
BMIF 310-Foundations of Bioinformatics and Computational Biology, 4 lectures, Fall 2010
BMIF 310-Foundations of Bioinformatics and Computational Biology, 1 lecture, Fall 2011

Research Supervision

Ph.D. Thesis Committee Member

Stephen VonStetina-Vanderbilt University (2001-2005)
Laura Wilding-Vanderbilt University (2003-2007)
Alex Statnikov-Vanderbilt University (2005-2008)
Alisha Russell-Vanderbilt University (2006-2010)
Mawuli Nyaku-University of Alabama-Birmingham (2010-2014)

M.S. Thesis Committee Member

Alex Statnikov (2003-2005)
Joel Parker (2000-2002)

Student Mentorship

Shristi Shrestha, PhD student (2014-present)
Nripesh Prasad, PhD student (2010-2014)
Sidd Pratrapp MS student (2005-2007)
Current position: Director of Bioinformatics, Meharry Medical College, Nashville, TN

Fellow Mentorship

Lewis Frey, PhD (2004-2006)
Current position: Assistant Professor, Department of Biomedical Informatics, University of Utah, Salt Lake City, UT.

Patents Awarded

Multiplex spatial profiling of gene expression
US 7,569,392 B2

Research Support

ACTIVE

NIH RFA-HG-16-011 (Cooper/Barsh/Korf) 06/01/2017 – 05/31/2021 0.60 calendar months
\$2,840,944

Clinical sequencing across communities in the Deep South

This proposal outlines an important study to apply WGS to diagnose neonates with rare disorders, increase participation of individuals from underrepresented racial/ethnic groups in genomics clinical trials, provide educational materials appropriate to diverse audiences, equip non-genetics healthcare providers to return WGS results, assess the impact of WGS testing and

results, and engage a broad community to implement safer, more effective, and more equitably distributed genomic medicine.

1U24HD090744-01 (Levy/Zhang) 09/23/2016 – 06/30/2019 2.40 calendar months
NIH/NICHD \$6,212,400

Characterizing pediatric genomes through an optimized sequencing approach

Understanding the fundamental genetic changes associated with structural birth defects and childhood cancers is an important step in developing tools to allow more advanced prediction, treatment and prevention of these devastating conditions. We propose to combine the resources of two world-class centers to support researchers in their investigations of the genetics of birth defects and childhood cancers. This centralized resource will provide researchers with the tools and support necessary to advance our understanding and drive us closer to curing or preventing these diseases.

5UL1TR001417-02 (Kimberly) 08/18/2015 - 03/31/2019 0.60 calendar months
NIH/NCATS \$83,644

UAB Center for Clinical and Translational Science (CCTS)

The UAB CCTS will enhance human health by driving scientific discovery and dialogue across the bench, bedside and community continuum. The CCTS support this overall mission in a highly integrative network of relationships. Success in creating such an environment is dependent upon success in achieving five strategic priorities: 1) enhancing research infrastructure; 2) promoting investigator education, training and development; 3) accelerating discovery across the T1 interface; 4) expanding value-added partnerships; and 5) building sustainability.

HHSN2722012000231 (Creech) 09/01/2015 – 09/30/2018 0.24 calendar months
NIH/NIAID \$555,660

Influenza A/H7N9 Vaccine Administered with/without AS03 Adjuvant: Standard and Systems Biology

HudsonAlpha will receive human RNA samples from Vanderbilt University Medical Center. RNA-sequencing will be performed per specifications provided in the clinical protocol and clarified in the manual of procedures. We will perform all necessary experiments, including quality control assays. Once sequencing data are obtained, these FastQ/BAM files will be transferred to Vanderbilt University Medical Center and to the DMID Statistics and Data Coordinating Center (SDCC) for data analysis.

HHSN2722012000231 (Creech) 09/01/2015 – 09/30/2018 0.24 calendar months
NIH/NIAID \$56,630

Sub-study for DMID 10-0074

HudsonAlpha will receive human RNA samples from Vanderbilt University Medical Center. RNA-sequencing will be performed per specifications provided in the clinical protocol and clarified in the manual of procedures. We will perform all necessary experiments, including quality control assays. Once sequencing data are obtained, these FastQ/BAM files will be transferred to Vanderbilt University Medical Center and to the DMID Statistics and Data Coordinating Center (SDCC) for data analysis.

6U19CA179514-05 (Coffey) 09/01/2013 - 08/31/2018 0.24 calendar months
NIH/NCI \$39,254

Secreted RNA during CRC progression biogenesis function and clinical markers

Dr. Levy's laboratory will fully support RNA sequencing on 48-74 samples per year prepared from either total RNA or microRNA at the HudsonAlpha Institute for Biotechnology. Dr. Levy's laboratory will provide all required reagents, personnel and basic analysis support for the

proposed sequencing studies during years 1-5 of the project period.

5U01MH105653-03 (Boehnke) 09/19/2014 - 05/31/2018 0.60 calendar months
NIH/NIMH \$23,557

Whole Genome Sequencing for Schizophrenia and Bipolar Disorder in the GPC

Dr. Levy will participate in weekly conference calls and several yearly face-to-face meetings to help make this project successful. Any new improvements in sequencing technology, data analysis and data interpretation that are developed and/or applied at HudsonAlpha will be made immediately available to this project.

3P30CA013145-44S4 (Partridge) 04/01/2017 – 03/31/2018 0.60 calendar months
NIH/NCI \$113,863

Comprehensive Cancer Center Core Support Grant

Dr. Myers, President and Science Director of HudsonAlpha Institute for Biotechnology, will be part of the director's council. The director's council meets on a monthly basis to advise the director on all major decisions regarding the UAB-CCC, its organization, planning and evaluation and to approve new developmental research programs and review program leaderships. In addition, Dr. Myers will co-lead UAB-CCC's Experimental Therapeutics program. Drs. Absher and Levy will be co-leaders of the Cancer Cell Biology Program and Cancer Control & Population Sciences Program. Dr. Cooper is an Associate Scientist in Experimental Therapeutics program. They will consult investigators in study design and analysis related to genomic data.

4UM1HG007301-04 (Cooper/Myers) 06/14/2013-05/31/2018(NCE)0.60 calendar months
NIH/NHGRI \$1,536,927

Genomic Diagnosis in Children with Developmental Delay

The goal of this project is to address technological, analytical, and ethical challenges that prevent optimal use of DNA sequencing to improve treatment of diseases and life planning for patients and their families. We are applying next-generation DNA sequencing to meet the diagnostic needs of children with developmental delay, intellectual disability and related health problems.

Genomic Services Lab Director 4.80 calendar months

In addition to the projects listed above, Dr. Levy, as the Director of the Genomic Services Laboratory (GSL), is involved in the development and application of genomic and bioinformatic technologies and methods to support scientific research. These activities, along with fee-for-service projects, change often making it difficult to assign a precise percent effort to individual projects. Dr. Levy has reviewed his GSL obligations and confirms that the aggregate effort on all GSL projects at any given time does not exceed 40% (4.80 calendar months) of institutional effort.

PENDING

COMPLETED

US MED Research ACQ Activity (PI: Richard M. Myers)

9/16/10 - 8/31/15

Direct Costs for current year: \$2,150,777

Shawn E. Levy effort: 33% effort [4.0 cal. mos.]

Title: Global genomic analysis of prostate, breast and pancreatic cancer

The goals of this study are to provide an unprecedented comprehensive view of the molecular pathogenesis of prostate, breast, and pancreatic cancer, as well as the differential response to treatments in breast cancer. We will use next-generation DNA sequencing to measure mRNA, microRNA, DNA methylation, DNase hypersensitivity sites, histone modifications, and sites of transcription factor occupancy in tumors and matched non-tumor tissues for these three cancers. No budgetary or scientific overlap.

Role: Co-investigator

NIH (PIs of Collaborative R01: Richard M. Myers and Michael Boehnke)

8/30/11 - 6/30/14

Direct costs for current year for HudsonAlpha portion: \$1,855,348

Shawn E. Levy effort: 20% [2.4 cal. mos.]

Title: Whole Genome and Exome Sequencing for Bipolar Disorder

In this collaborative R01 grant, performed jointly with Dr. Michael Boehnke and colleagues at the University of Michigan, we are performing a detailed genetic analysis of bipolar disorder. We are using ultrahigh-throughput sequencing to determine the deep whole genome sequences from 1,000 individuals with bipolar disorder and 1,000 control individuals without the disorder.

NIH/NIAMS 1 R01 AR057202 (PI: Louis Bridges)

4/1/09 - 3/31/14

Direct Costs for current year for Myers/Absher portion: \$298,704

Shawn E. Levy effort: 5% effort [0.60 cal mos.]

Title: Genome Wide Association Study in African-Americans with Rheumatoid Arthritis

In this study, the Myers lab and Devin Absher and his lab at HudsonAlpha are collaborating with Dr. Lou Bridges and his colleagues at the School of Medicine at the University of Alabama in Birmingham to perform a genome-wide genetic association study of rheumatoid arthritis in African Americans. No budgetary or scientific overlap.

Role: Co-investigator

NHGRI P50 HG02568 (PI: David Kingsley)

4/19/02 - 5/31/12

Direct costs for current year: \$701,981

Shawn E. Levy effort: 10% effort [1.2 cal. mos.]

Title: Center for Vertebrate Diversity

The continuation of this Center of Excellence in Genome Science (CEGS) has broad goals to understand the genetic basis for the striking biological diversity seen in vertebrate animals. We use genetics, genomics, molecular biology and computational tools to study this problem, focusing on the three-spined stickleback fish. HudsonAlpha performs many of the genomic experiments for this project, including genomic DNA sequencing, cDNA sequencing, BAC map construction, and genotyping.

Role: Co-investigator

5 U54 HG004576-03 (Myers)

10/01/2007 – 09/30/2011

1.20 calendar

NIH/NHGRI

\$3,985,643

“Global Annotation of Regulatory Elements in the Human Genome”

This project, which is a collaboration between the Myers group at HudsonAlpha and Barbara Wold's group at Caltech, along with contributions from Wing Wong, Arend Sidow, Serafim Batzoglou and Gavin Sherlock at Stanford, is part of the ENCODE Project, whose goals are to identify and understand the roles of all the functional elements throughout the entire human

genome. Our contributions are to identify transcription factor binding sites, assess the methylation status and measure RNAs with next-gen sequencing.

Role: Co-investigator

1 RC1 DK086594-01 (Southard-Smith)

09/30/2009 – 09/29/2011

0.60 calendar months

NIH

\$240,970

“Gene Networks in Neural Crest-derived Innervation of the Lower Urinary Tract”

The studies proposed aim to identify essential genes that control development of nerves in the lower urinary tract that regulate bladder control and sexual function. These studies are important for understanding how these nerves normally develop and for deriving technologies that will restore neural function in urogenital birth defects or after pelvic surgery. This proposal is in response to the broad Challenge grant area of Regenerative medicine and meets multiple needs for basic research in development lower urinary tract innervation.

Role: Co-investigator

5 P30 CA68485-13 (Pietenpol)

09/28/2004 - 08/31/2009

1.80 calendar months

NIH/NCI

\$3,553,801

“Cancer Center Support Grant”

As part of the Vanderbilt Ingram Cancer Center’s support grant, the goal of the Microarray Core is to provide genome-scale expression profiling technologies as well as analysis and informatics support to researchers who are members of the center.

5 P30DK058404-07 (Polk)

08/30/2007 - 05/31/2012

1.20 calendar months

NIH/NIDDK

\$727,500

“Molecular and Cellular Basis of Digestive Diseases”

As part of a center grant, the goal of the Microarray Core in the Vanderbilt Digestive Diseases Center is to provide support for the use of genome-scale expression profiling technologies to researchers involved in digestive disease-related research.

Role: Core Leader

5 P60 DK20593-31 (Powers)

06/01/2007 - 03/31/2012

0.24 calendar months

NIH/NIDDK

\$1,487,659

“Diabetes Research and Training Center”

As part of a center grant, the goal of the Microarray and Bioinformatics Core in the Diabetes Research and Training Center is to provide support for the use of genome-scale expression profiling technologies to researchers involved in DRTC-related research.

Role: Core Leader

2 R01 CA064277-10A1 (Zheng)

08/05/2008 - 05/31/2013

0.24 calendar months

NIH/NCI

\$324,917

“Shanghai Breast Cancer Study”

This proposal is aimed at the development of novel algorithms for the analysis of high-dimensionality data towards to the discovery of causal markers and mechanisms.

Role: Co-investigator

5 U24 DK58749-03 (George)

09/30/00 - 08/31/03

1.2 calendar months

NIH/NIDDK

Vanderbilt NIDDK Biotechnology Center

Purpose: The goal of this proposal was the establishment of a Biotechnology Center for the support of genomic studies of interest to investigators funded by the NIDDK. Microarray technologies and related informatics were central to the efforts.

Role: Co-investigator

VUMC Discovery Grant 540 (Levy)

01/01/02 - 12/31/03

1.2 calendar months

VUMC Internal Grant

\$50,000

Gene Expression Analysis of Colon Cancer

The goal of this proposal was the development of an integrated RNA and protein expression profile for colon cancer utilizing microarray and high-resolution protein profiling technologies. These profiles were useful in designing and developing both technological and informatic platforms for the combined analysis of protein and genetic profiles of cancer.

Role: Principle Investigator

ACS IRG-58-009-46 (Levy)

07/01/03 - 06/30/04

ACS/VICC

Simultaneous profiling of protein and RNA expression by mass spectrometry in intact tissue sections.

The goal of this proposal is to develop a novel technology platform that facilitates the simultaneous profiling of protein and RNA species in intact tissue samples while reporting spatial position. This will provide an unprecedented resolution to examine the biology of tumor samples and host-tumor interactions.

Role: Principle Investigator

1 R21 NS043581-01A1 (McDonald)

12/01/02 - 11/30/04

NIH/NINDS

Gene Discovery in a Putative Mouse Model of ADHD

In this proposal, microarray technology will be used to examine differential gene expression in the mouse model of ADHD, providing a rare opportunity to discover genes downstream of TR β activity that are able to produce all of the core symptoms and many adjunct features of ADHD.

Role: Co-investigator

1 U01 DK063587-01 (Hayward)

09/30/02 - 06/30/05

NIH/NIDDK

Genetic Markers of Transition Zone Hyperplasia

The goals of this proposal are the identification of biomarkers for prostate hyperplasia through the use of high-density microarray studies on novel models of prostate disease.

Role: Co-investigator

W81XWH-04-1-0626 (Levy S)

07/15/04-07/14/06

Department of Defense

Simultaneous profiling of protein and RNA expression by mass spectrometry in intact breast tissue sections.

The goal of this proposal is to continue the development of a novel technology platform that facilitates the simultaneous profiling of protein and RNA species in intact tissue samples while reporting spatial position. This proposal will specifically fund the optimization of this technology for the analysis of breast tissue samples.

Role: Principle Investigator

5 P01 HL6744-04 (Hawiger J)

12/01/01-11/30/06

NIH/NHLBI

Functional Genomics of Inflammation

As part of a Program Project Grant, the goal of the Microarray Core in the Functional Genomics of Inflammation program project is to provide genome-scale expression profiling technologies to researchers involved in the program.

Role: Core Leader

1 R01 DK068261-01 (Nagy T)

07/01/04-06/30/07

NIH/NIDDK (subcontract with UT)

Antipsychotic Drug-induced Weight Gain

The goal of this study is to understand the actions of antipsychotic drugs as they alter body weight. In this short subcontract with the University of Alabama, an animal model system used to study the molecular effects of selected drugs will be analyzed using genomic profiling techniques.

Role: Principal Investigator-subcontract

5 P60 DK20593-27 (Powers A)

07/20/02-03/31/07

NIH/NIDDK

Diabetes Research and Training Center-Microarray and Bioinformatics Core

As part of a center grant, the goal of the Microarray Core in the Diabetes Research and Training Center is to provide support for the use of genome-scale expression profiling technologies to researchers involved in DRTC-related research.

Role: Core Leader

5 P50 CA95103-04 (Coffey RJ)

09/24/02-04/30/07

NIH/NCI

SPORE in GI Cancer

This study will investigate the molecular features of tumors in GI cancer and provide full support for genomic profiling projects as part of the overall SPORE program.

Role: Core Leader

U24 CA126563 (Myers)

09/28/06 – 08/31/10

NIH/NCI

"The HudsonAlpha Cancer Genome Characterization Center

We are characterizing tumors and matched non-tumor samples for copy number variations throughout the human genome as part of The Cancer Genome Atlas project, a trans-NIH initiative aimed at learning all the genetic and genomic changes associated with cancer. We use a whole-genome genotyping method to assay more than 1 million SNPs throughout the genome.

Role: Co-investigator

1 RC1 HL100016-01 (Schey)

09/30/09 – 09/29/11

NIH-ARRA Funding

“Proteome and Transcriptome Markers of Hypertension in Urine and Plasma Exosomes”

The goal of the proposed research is to develop a novel method for discovery of molecular markers of disease that circumvents existing obstacles. Through analysis of proteins and RNA found in lipid particles isolated from blood and urine, new markers of disease will be discovered that improve diagnosis, prognosis, and prediction of response to therapy; that is, improve personalized medicine. The new methodology will be applied to reveal biomarkers of salt-sensitivity and therapeutic response in hypertensive subjects.

Role: Co-investigator

Publications

162 peer-reviewed publications with a total of 23,891 citations (as of October 2018).

A full publication and patent listing can be accessed via a public Google Scholar profile at:

<http://scholar.google.com/citations?user=xeKJAZ0AAAAJ>

As well as at NCBI:

<http://www.ncbi.nlm.nih.gov/sites/myncbi/1BODvQqGn4iAa/bibliography/43127950/public/>

Articles in refereed journals

1. Levy SE, Waymire KG, Kim YL, MacGregor GR, Wallace DC. Transfer of chloramphenicol-resistant mitochondrial DNA into the chimeric mouse. **Transgenic Res.** 1999;8(2):137-145. PubMed PMID: 10481313; PMCID: PMC3049807.
2. Levy SE, Chen YS, Graham BH, Wallace DC. Expression and sequence analysis of the mouse adenine nucleotide translocase 1 and 2 genes. **Gene.** 2000;254(1-2):57-66. PubMed PMID: 10974536.
3. Sligh JE, Levy SE, Waymire KG, Allard P, Dillehay DL, Nusinowitz S, Heckenlively JR, MacGregor GR, Wallace DC. Maternal germ-line transmission of mutant mtDNAs from embryonic stem cell-derived chimeric mice. **Proc Natl Acad Sci U S A.** 2000;97(26):14461-14466. doi: 10.1073/pnas.250491597. PubMed PMID: 11106380; PMCID: PMC18941.
4. Levy SE, Muldowney JA, 3rd. Microarray analysis of neointima: flowing toward a clear future. **Arterioscler Thromb Vasc Biol.** 2002;22(12):1946-1947. PubMed PMID: 12482816.
5. Park Y-K, Franklin JL, Settle SH, Levy SE, Whitehead RH, Coffey RJ. Microarray gene expression profiling and correlation with morphological changes during mouse colonic development. **Gastroenterology.** 2003;124(4):A602.

6. Gu G, Deutch AY, Franklin J, Levy S, Wallace DC, Zhang J. Profiling genes related to mitochondrial function in mice treated with N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. **Biochem Biophys Res Commun**. 2003;308(1):197-205. PubMed PMID: 12890501.
7. Yamagata N, Shyr Y, Yanagisawa K, Edgerton M, Dang TP, Gonzalez A, Nadaf S, Larsen P, Roberts JR, Nesbitt JC, Jensen R, Levy S, Moore JH, Minna JD, Carbone DP. A training-testing approach to the molecular classification of resected non-small cell lung cancer. **Clin Cancer Res**. 2003;9(13):4695-4704. PubMed PMID: 14581339.
8. Levy SE. Microarray analysis in drug discovery: an uplifting view of depression. **Sci STKE**. 2003;2003(206):pe46. doi: 10.1126/stke.2003.206.pe46. PubMed PMID: 14583588.
9. McQuain MK, Seale K, Peek J, Levy S, Haselton FR. Effects of relative humidity and buffer additives on the contact printing of microarrays by quill pins. **Anal Biochem**. 2003;320(2):281-291. PubMed PMID: 12927835.
10. McQuain MK, Seale K, Peek J, Fisher TS, Levy S, Stremmler MA, Haselton FR. Chaotic mixer improves microarray hybridization. **Anal Biochem**. 2004;325(2):215-226. PubMed PMID: 14751256.
11. Law AK, Gupta D, Levy S, Wallace DC, McKeon RJ, Buck CR. TGF-beta1 induction of the adenine nucleotide translocator 1 in astrocytes occurs through Smads and Sp1 transcription factors. **BMC Neurosci**. 2004;5:1. doi: 10.1186/1471-2202-5-1. PubMed PMID: 14720305; PMCID: PMC324399.
12. Kokoszka JE, Waymire KG, Levy SE, Sligh JE, Cai J, Jones DP, MacGregor GR, Wallace DC. The ADP/ATP translocator is not essential for the mitochondrial permeability transition pore. **Nature**. 2004;427(6973):461-465. doi: 10.1038/nature02229. PubMed PMID: 14749836; PMCID: PMC3049806.
13. Sforza DM, Annese J, Liu D, Levy S, Toga AW, Smith DJ. Anatomical methods for voxelation of the mammalian brain. **Neurochem Res**. 2004;29(6):1299-1306. PubMed PMID: 15176486.
14. Friedman DB, Hill S, Keller JW, Merchant NB, Levy SE, Coffey RJ, Caprioli RM. Proteome analysis of human colon cancer by two-dimensional difference gel electrophoresis and mass spectrometry. **Proteomics**. 2004;4(3):793-811. doi: 10.1002/pmic.200300635. PubMed PMID: 14997500.
15. Chung C, Carter J, Ely K, Murphy B, Burkey B, Netterville J, Levy S, Cmelak A, Slebos R, Yarbrough W. Gene expression analysis of head and neck squamous cell carcinoma using formalin-fixed paraffin embedded tissue. **Journal of Clinical Oncology**. 2005;23(16_suppl):5537-5537.
16. Levy SE, Statnikov A, Aliferis C. Biomarker selection from high-dimensionality data. **Pharmaceutical Discovery**. 2005;5(7):S37-S37.
17. Park YK, Franklin JL, Settle SH, Levy SE, Chung E, Jeyakumar LH, Shyr Y, Washington MK, Whitehead RH, Aronow BJ, Coffey RJ. Gene expression profile analysis of mouse colon embryonic development. **Genesis**. 2005;41(1):1-12. doi: 10.1002/gene.20088. PubMed PMID: 15645444.
18. Statnikov A, Aliferis CF, Tsamardinos I, Hardin D, Levy S. A comprehensive evaluation of multicategory classification methods for microarray gene expression cancer diagnosis. **Bioinformatics**. 2005;21(5):631-643. doi: 10.1093/bioinformatics/bti033. PubMed PMID: 15374862.

19. Xie L, Xu BJ, Gorska AE, Shyr Y, Schwartz SA, Cheng N, Levy S, Bieri B, Caprioli RM, Moses HL. Genomic and proteomic analysis of mammary tumors arising in transgenic mice. **J Proteome Res.** 2005;4(6):2088-2098. doi: 10.1021/pr050214l. PubMed PMID: 16335954.
20. Chung CH, Levy S, Yarbrough WG. Clinical applications of genomics in head and neck cancer. **Head Neck.** 2006;28(4):360-368. doi: 10.1002/hed.20323. PubMed PMID: 16284976.
21. Acuff HB, Sinnamon M, Fingleton B, Boone B, Levy SE, Chen X, Pozzi A, Carbone DP, Schwartz DR, Moin K, Sloane BF, Matrisian LM. Analysis of host- and tumor-derived proteinases using a custom dual species microarray reveals a protective role for stromal matrix metalloproteinase-12 in non-small cell lung cancer. **Cancer Res.** 2006;66(16):7968-7975. doi: 10.1158/0008-5472.CAN-05-4279. PubMed PMID: 16912171.
22. Chung CH, Parker JS, Ely K, Carter J, Yi Y, Murphy BA, Ang KK, El-Naggar AK, Zanation AM, Cmelak AJ, Levy S, Slebos RJ, Yarbrough WG. Gene expression profiles identify epithelial-to-mesenchymal transition and activation of nuclear factor-kappaB signaling as characteristics of a high-risk head and neck squamous cell carcinoma. **Cancer Res.** 2006;66(16):8210-8218. doi: 10.1158/0008-5472.CAN-06-1213. PubMed PMID: 16912200.
23. Slebos RJ, Yi Y, Ely K, Carter J, Evjen A, Zhang X, Shyr Y, Murphy BM, Cmelak AJ, Burkey BB, Netterville JL, Levy S, Yarbrough WG, Chung CH. Gene expression differences associated with human papillomavirus status in head and neck squamous cell carcinoma. **Clin Cancer Res.** 2006;12(3 Pt 1):701-709. doi: 10.1158/1078-0432.CCR-05-2017. PubMed PMID: 16467079.
24. Consortium M, Shi L, Reid LH, Jones WD, Shippy R, Warrington JA, Baker SC, Collins PJ, de Longueville F, Kawasaki ES, Lee KY, Luo Y, Sun YA, Willey JC, Setterquist RA, Fischer GM, Tong W, Dragan YP, Dix DJ, Frueh FW, Goodsaid FM, Herman D, Jensen RV, Johnson CD, Lobenhofer EK, Puri RK, Schrf U, Thierry-Mieg J, Wang C, Wilson M, Wolber PK, Zhang L, Amur S, Bao W, Barbacioru CC, Lucas AB, Bertholet V, Boysen C, Bromley B, Brown D, Brunner A, Canales R, Cao XM, Cebula TA, Chen JJ, Cheng J, Chu TM, Chudin E, Corson J, Corton JC, Croner LJ, Davies C, Davison TS, Delenstarr G, Deng X, Dorris D, Eklund AC, Fan XH, Fang H, Fulmer-Smentek S, Fuscoe JC, Gallagher K, Ge W, Guo L, Guo X, Hager J, Haje PK, Han J, Han T, Harbottle HC, Harris SC, Hatchwell E, Hauser CA, Hester S, Hong H, Hurban P, Jackson SA, Ji H, Knight CR, Kuo WP, LeClerc JE, Levy S, Li QZ, Liu C, Liu Y, Lombardi MJ, Ma Y, Magnuson SR, Maqsoodi B, McDaniel T, Mei N, Myklebost O, Ning B, Novorodovskaya N, Orr MS, Osborn TW, Papallo A, Patterson TA, Perkins RG, Peters EH, Peterson R, Philips KL, Pine PS, Pusztai L, Qian F, Ren H, Rosen M, Rosenzweig BA, Samaha RR, Schena M, Schroth GP, Shchegrova S, Smith DD, Staedtler F, Su Z, Sun H, Szallasi Z, Tezak Z, Thierry-Mieg D, Thompson KL, Tikhonova I, Turpaz Y, Vallanat B, Van C, Walker SJ, Wang SJ, Wang Y, Wolfinger R, Wong A, Wu J, Xiao C, Xie Q, Xu J, Yang W, Zhang L, Zhong S, Zong Y, Slikker W, Jr. The MicroArray Quality Control (MAQC) project shows inter- and intraplatform reproducibility of gene expression measurements. **Nat Biotechnol.** 2006;24(9):1151-1161. doi: 10.1038/nbt1239. PubMed PMID: 16964229; PMCID: PMC3272078.
25. Chung CH, Ely K, McGavran L, Varella-Garcia M, Parker J, Parker N, Jarrett C, Carter J, Murphy BA, Netterville J, Burkey BB, Sinard R, Cmelak A, Levy S, Yarbrough WG, Slebos RJ, Hirsch FR. Increased epidermal growth factor receptor gene copy number is associated with poor prognosis in head and neck squamous cell carcinomas. **J Clin Oncol.** 2006;24(25):4170-4176. doi: 10.1200/JCO.2006.07.2587. PubMed PMID: 16943533.

26. Chung CH, Parker J, Levy S, Slebos RJ, Dicker AP, Rodeck U. Gene expression profiles as markers of aggressive disease-EGFR as a factor. **Int J Radiat Oncol Biol Phys**. 2007;69(2 Suppl):S102-105. doi: 10.1016/j.ijrobp.2007.05.039. PubMed PMID: 17848272; PMCID: PMC2361130.
27. Frey L, Edgerton M, Fisher D, Levy S. Ensemble stump classifiers and gene expression signatures in lung cancer. **Stud Health Technol Inform**. 2007;129(Pt 2):1255-1259. PubMed PMID: 17911916.
28. Kaiser S, Park YK, Franklin JL, Halberg RB, Yu M, Jessen WJ, Freudenberg J, Chen X, Haigis K, Jegga AG, Kong S, Sakthivel B, Xu H, Reichling T, Azhar M, Boivin GP, Roberts RB, Bissahoyo AC, Gonzales F, Bloom GC, Eschrich S, Carter SL, Aronow JE, Kleimyer J, Kleimyer M, Ramaswamy V, Settle SH, Boone B, Levy S, Graff JM, Doetschman T, Groden J, Dove WF, Threadgill DW, Yeatman TJ, Coffey RJ, Jr., Aronow BJ. Transcriptional recapitulation and subversion of embryonic colon development by mouse colon tumor models and human colon cancer. **Genome Biol**. 2007;8(7):R131. doi: 10.1186/gb-2007-8-7-r131. PubMed PMID: 17615082; PMCID: PMC2323222.
29. Zhou S, Wei S, Boone B, Levy S. Microarray analysis of genes affected by salt stress in tomato. **African Journal of Environmental Science and Technology**. 2007;1(2):14-26.
30. Chin MH, Geng AB, Khan AH, Qian WJ, Petyuk VA, Boline J, Levy S, Toga AW, Smith RD, Leahy RM, Smith DJ. A genome-scale map of expression for a mouse brain section obtained using voxelation. **Physiol Genomics**. 2007;30(3):313-321. doi: 10.1152/physiolgenomics.00287.2006. PubMed PMID: 17504947; PMCID: PMC3299369.
31. Muldowney JA, 3rd, Stringham JR, Levy SE, Gleaves LA, Eren M, Piana RN, Vaughan DE. Antiproliferative agents alter vascular plasminogen activator inhibitor-1 expression: a potential prothrombotic mechanism of drug-eluting stents. **Arterioscler Thromb Vasc Biol**. 2007;27(2):400-406. doi: 10.1161/01.ATV.0000254677.12861.b8. PubMed PMID: 17158352.
32. Chung CH, Levy S, Chaurand P, Carbone DP. Genomics and proteomics: emerging technologies in clinical cancer research. **Crit Rev Oncol Hematol**. 2007;61(1):1-25. doi: 10.1016/j.critrevonc.2006.06.005. PubMed PMID: 17015021.
33. Joshi S, Davies H, Sims LP, Levy SE, Dean J. Ovarian gene expression in the absence of FIGLA, an oocyte-specific transcription factor. **BMC Dev Biol**. 2007;7:67. doi: 10.1186/1471-213X-7-67. PubMed PMID: 17567914; PMCID: PMC1906760.
34. Zhou S, Sauvé R, Boone B, Levy S. Identification of genes associated with aluminium toxicity in tomato roots using cDNA microarrays. **Plant Stress**. 2008;2(2):113-120.
35. Pratap S, Williams SM, Levy SE. Evaluation of pooled allelotyping versus individual genotyping for genome-wide association analysis of complex disease. **BMC Bioinformatics**. 2008;9(7):P11.
36. Beeghly-Fadiel A, Long JR, Gao YT, Li C, Qu S, Cai Q, Zheng Y, Ruan ZX, Levy SE, Deming SL, Snoddy JR, Shu XO, Lu W, Zheng W. Common MMP-7 polymorphisms and breast cancer susceptibility: a multistage study of association and functionality. **Cancer Res**. 2008;68(15):6453-6459. doi: 10.1158/0008-5472.CAN-08-0636. PubMed PMID: 18648013; PMCID: PMC2718434.
37. Watson JD, Wang S, Von Stetina SE, Spencer WC, Levy S, Dexheimer PJ, Kurn N, Heath JD, Miller DM, 3rd. Complementary RNA amplification methods enhance microarray identification of transcripts expressed in the *C. elegans* nervous system. **BMC Genomics**.

- 2008;9:84. doi: 10.1186/1471-2164-9-84. PubMed PMID: 18284693; PMCID: PMC2263045.
38. Wilding Crawford L, Tweedie Ables E, Oh YA, Boone B, Levy S, Gannon M. Gene expression profiling of a mouse model of pancreatic islet dysmorphogenesis. **PLoS One**. 2008;3(2):e1611. doi: 10.1371/journal.pone.0001611. PubMed PMID: 18297134; PMCID: PMC2249940.
39. Kanies CL, Smith JJ, Kis C, Schmidt C, Levy S, Khabar KS, Morrow J, Deane N, Dixon DA, Beauchamp RD. Oncogenic Ras and transforming growth factor-beta synergistically regulate AU-rich element-containing mRNAs during epithelial to mesenchymal transition. **Mol Cancer Res**. 2008;6(7):1124-1136. doi: 10.1158/1541-7786.MCR-07-2095. PubMed PMID: 18644977; PMCID: PMC2572152.
40. Xu B, Roos JL, Levy S, van Rensburg EJ, Gogos JA, Karayiorgou M. Strong association of de novo copy number mutations with sporadic schizophrenia. **Nat Genet**. 2008;40(7):880-885. doi: 10.1038/ng.162. PubMed PMID: 18511947.
41. Subramaniam V, Golik P, Murdock DG, Levy S, Kerstann KW, Coskun PE, Melkonian GA, Wallace DC. MITOCHIP assessment of differential gene expression in the skeletal muscle of Ant1 knockout mice: coordinate regulation of OXPHOS, antioxidant, and apoptotic genes. **Biochim Biophys Acta**. 2008;1777(7-8):666-675. doi: 10.1016/j.bbabi.2008.03.015. PubMed PMID: 18439414; PMCID: PMC4391341.
42. Liu YJ, Liu XG, Wang L, Dina C, Yan H, Liu JF, Levy S, Papasian CJ, Drees BM, Hamilton JJ, Meyre D, Delplanque J, Pei YF, Zhang L, Recker RR, Froguel P, Deng HW. Genome-wide association scans identified CTNBL1 as a novel gene for obesity. **Hum Mol Genet**. 2008;17(12):1803-1813. doi: 10.1093/hmg/ddn072. PubMed PMID: 18325910; PMCID: PMC2900891.
43. Liu YZ, Wilson SG, Wang L, Liu XG, Guo YF, Li J, Yan H, Deloukas P, Soranzo N, Chinapen-Horsley U, Cervino A, Williams FM, Xiong DH, Zhang YP, Jin TB, Levy S, Papasian CJ, Drees BM, Hamilton JJ, Recker RR, Spector TD, Deng HW. Identification of PLCL1 gene for hip bone size variation in females in a genome-wide association study. **PLoS One**. 2008;3(9):e3160. doi: 10.1371/journal.pone.0003160. PubMed PMID: 18776929; PMCID: PMC2522269.
44. Hatakeyama H, Parker J, Wheeler D, Harari P, Levy S, Chung C. Effect of insulin-like growth factor 1 receptor inhibitor on sensitization of head and neck cancer cells to cetuximab and methotrexate. **Journal of Clinical Oncology**. 2009;27(15S):6079-6079.
45. Liu Y-Z, Pei Y-F, Liu J-F, Yang F, Guo Y, Zhang L, Liu X-G, Yan H, Wang L, Zhang Y-P. Powerful bivariate genome-wide association analyses suggest the SOX6 gene influencing both obesity and osteoporosis phenotypes in males. **PloS One**. 2009;4(8):e6827.
46. Liu YZ, Pei YF, Liu JF, Yang F, Guo Y, Zhang L, Liu XG, Yan H, Wang L, Zhang YP, Levy S, Recker RR, Deng HW. Powerful bivariate genome-wide association analyses suggest the SOX6 gene influencing both obesity and osteoporosis phenotypes in males. **PLoS One**. 2009;4(8):e6827. doi: 10.1371/journal.pone.0006827. PubMed PMID: 19714249; PMCID: PMC2730014.
47. Liu YZ, Pei YF, Guo YF, Wang L, Liu XG, Yan H, Xiong DH, Zhang YP, Levy S, Li J, Haddock CK, Papasian CJ, Xu Q, Ma JZ, Payne TJ, Recker RR, Li MD, Deng HW. Genome-wide association analyses suggested a novel mechanism for smoking behavior regulated by IL15. **Mol Psychiatry**. 2009;14(7):668-680. doi: 10.1038/mp.2009.3. PubMed PMID: 19188921; PMCID: PMC2700850.

48. Zheng W, Long J, Gao YT, Li C, Zheng Y, Xiang YB, Wen W, Levy S, Deming SL, Haines JL, Gu K, Fair AM, Cai Q, Lu W, Shu XO. Genome-wide association study identifies a new breast cancer susceptibility locus at 6q25.1. **Nat Genet.** 2009;41(3):324-328. doi: 10.1038/ng.318. PubMed PMID: 19219042; PMCID: PMC2754845.
49. Xiong DH, Liu XG, Guo YF, Tan LJ, Wang L, Sha BY, Tang ZH, Pan F, Yang TL, Chen XD, Lei SF, Yerges LM, Zhu XZ, Wheeler VW, Patrick AL, Bunker CH, Guo Y, Yan H, Pei YF, Zhang YP, Levy S, Papasian CJ, Xiao P, Lundberg YW, Recker RR, Liu YZ, Liu YJ, Zmuda JM, Deng HW. Genome-wide association and follow-up replication studies identified ADAMTS18 and TGFBR3 as bone mass candidate genes in different ethnic groups. **Am J Hum Genet.** 2009;84(3):388-398. doi: 10.1016/j.ajhg.2009.01.025. PubMed PMID: 19249006; PMCID: PMC2667986.
50. Liu YZ, Guo YF, Wang L, Tan LJ, Liu XG, Pei YF, Yan H, Xiong DH, Deng FY, Yu N, Zhang YP, Zhang L, Lei SF, Chen XD, Liu HB, Zhu XZ, Levy S, Papasian CJ, Drees BM, Hamilton JJ, Recker RR, Deng HW. Genome-wide association analyses identify SPOCK as a key novel gene underlying age at menarche. **PLoS Genet.** 2009;5(3):e1000420. doi: 10.1371/journal.pgen.1000420. PubMed PMID: 19282985; PMCID: PMC2652107.
51. Liu XG, Tan LJ, Lei SF, Liu YJ, Shen H, Wang L, Yan H, Guo YF, Xiong DH, Chen XD, Pan F, Yang TL, Zhang YP, Guo Y, Tang NL, Zhu XZ, Deng HY, Levy S, Recker RR, Papasian CJ, Deng HW. Genome-wide association and replication studies identified TRHR as an important gene for lean body mass. **Am J Hum Genet.** 2009;84(3):418-423. doi: 10.1016/j.ajhg.2009.02.004. PubMed PMID: 19268274; PMCID: PMC2668008.
52. Lei SF, Tan LJ, Liu XG, Wang L, Yan H, Guo YF, Liu YZ, Xiong DH, Li J, Yang TL, Chen XD, Guo Y, Deng FY, Zhang YP, Zhu XZ, Levy S, Papasian CJ, Hamilton JJ, Recker RR, Deng HW. Genome-wide association study identifies two novel loci containing FLNB and SBF2 genes underlying stature variation. **Hum Mol Genet.** 2009;18(9):1661-1669. doi: 10.1093/hmg/ddn405. PubMed PMID: 19039035; PMCID: PMC2667283.
53. Li J, Yang T, Wang L, Yan H, Zhang Y, Guo Y, Pan F, Zhang Z, Peng Y, Zhou Q, He L, Zhu X, Deng H, Levy S, Papasian CJ, Drees BM, Hamilton JJ, Recker RR, Cheng J, Deng HW. Whole genome distribution and ethnic differentiation of copy number variation in Caucasian and Asian populations. **PLoS One.** 2009;4(11):e7958. doi: 10.1371/journal.pone.0007958. PubMed PMID: 19956714; PMCID: PMC2776354.
54. De Moor MH, Liu YJ, Boomsma DI, Li J, Hamilton JJ, Hottenga JJ, Levy S, Liu XG, Pei YF, Posthuma D, Recker RR, Sullivan PF, Wang L, Willemsen G, Yan H, De Geus EJ, Deng HW. Genome-wide association study of exercise behavior in Dutch and American adults. **Med Sci Sports Exerc.** 2009;41(10):1887-1895. doi: 10.1249/MSS.0b013e3181a2f646. PubMed PMID: 19727025; PMCID: PMC2895958.
55. Canter JA, Robbins GK, Selph D, Clifford DB, Kallianpur AR, Shafer R, Levy S, Murdock DG, Ritchie MD, Haas DW, Hulgand T, Team ACTGS, New Work Concept Sheet T. African mitochondrial DNA subhaplogroups and peripheral neuropathy during antiretroviral therapy. **J Infect Dis.** 2010;201(11):1703-1707. doi: 10.1086/652419. PubMed PMID: 20402593; PMCID: PMC2862090.
56. Greco JA, 3rd, Pollins AC, Boone BE, Levy SE, Nanney LB. A microarray analysis of temporal gene expression profiles in thermally injured human skin. **Burns.** 2010;36(2):192-204. doi: 10.1016/j.burns.2009.06.211. PubMed PMID: 19781859; PMCID: PMC3755600.
57. Smith JJ, Deane NG, Wu F, Merchant NB, Zhang B, Jiang A, Lu P, Johnson JC, Schmidt C, Bailey CE, Eschrich S, Kis C, Levy S, Washington MK, Heslin MJ, Coffey RJ, Yeatman

- TJ, Shyr Y, Beauchamp RD. Experimentally derived metastasis gene expression profile predicts recurrence and death in patients with colon cancer. **Gastroenterology**. 2010;138(3):958-968. doi: 10.1053/j.gastro.2009.11.005. PubMed PMID: 19914252; PMCID: PMC3388775.
58. Motsinger-Reif AA, Antas PR, Oki NO, Levy S, Holland SM, Sterling TR. Polymorphisms in IL-1beta, vitamin D receptor Fok1, and Toll-like receptor 2 are associated with extrapulmonary tuberculosis. **BMC Med Genet**. 2010;11:37. doi: 10.1186/1471-2350-11-37. PubMed PMID: 20196868; PMCID: PMC2837863.
 59. Lange LA, Croteau-Chonka DC, Marvelle AF, Qin L, Gaulton KJ, Kuzawa CW, McDade TW, Wang Y, Li Y, Levy S, Borja JB, Lange EM, Adair LS, Mohlke KL. Genome-wide association study of homocysteine levels in Filipinos provides evidence for CPS1 in women and a stronger MTHFR effect in young adults. **Hum Mol Genet**. 2010;19(10):2050-2058. doi: 10.1093/hmg/ddq062. PubMed PMID: 20154341; PMCID: PMC2860887.
 60. Otto EA, Hurd TW, Airik R, Chaki M, Zhou W, Stoetzel C, Patil SB, Levy S, Ghosh AK, Murga-Zamalloa CA, van Reeuwijk J, Letteboer SJ, Sang L, Giles RH, Liu Q, Coene KL, Estrada-Cuzcano A, Collin RW, McLaughlin HM, Held S, Kasanuki JM, Ramaswami G, Conte J, Lopez I, Washburn J, Macdonald J, Hu J, Yamashita Y, Maher ER, Guay-Woodford LM, Neumann HP, Obermuller N, Koenekoop RK, Bergmann C, Bei X, Lewis RA, Katsanis N, Lopes V, Williams DS, Lyons RH, Dang CV, Brito DA, Dias MB, Zhang X, Cavalcoli JD, Nurnberg G, Nurnberg P, Pierce EA, Jackson PK, Antignac C, Saunier S, Roepman R, Dollfus H, Khanna H, Hildebrandt F. Candidate exome capture identifies mutation of SDCCAG8 as the cause of a retinal-renal ciliopathy. **Nat Genet**. 2010;42(10):840-850. doi: 10.1038/ng.662. PubMed PMID: 20835237; PMCID: PMC2947620.
 61. Tan L, Liu R, Lei S, Pan R, Yang T, Yan H, Pei Y, Yang F, Zhang F, Pan F, Zhang Y, Hu H, Levy S, Deng H. A genome-wide association analysis implicates SOX6 as a candidate gene for wrist bone mass. **Sci China Life Sci**. 2010;53(9):1065-1072. doi: 10.1007/s11427-010-4056-7. PubMed PMID: 21104366.
 62. Xu B, Roos JL, Dexheimer P, Boone B, Plummer B, Levy S, Gogos JA, Karayiorgou M. Exome sequencing supports a de novo mutational paradigm for schizophrenia. **Nat Genet**. 2011;43(9):864-868. doi: 10.1038/ng.902. PubMed PMID: 21822266; PMCID: PMC3196550.
 63. Cai Q, Long J, Lu W, Qu S, Wen W, Kang D, Lee JY, Chen K, Shen H, Shen CY, Sung H, Matsuo K, Haiman CA, Khoo US, Ren Z, Iwasaki M, Gu K, Xiang YB, Choi JY, Park SK, Zhang L, Hu Z, Wu PE, Noh DY, Tajima K, Henderson BE, Chan KY, Su F, Kasuga Y, Wang W, Cheng JR, Yoo KY, Lee JY, Zheng H, Liu Y, Shieh YL, Kim SW, Lee JW, Iwata H, Le Marchand L, Chan SY, Xie X, Tsugane S, Lee MH, Wang S, Li G, Levy S, Huang B, Shi J, Delahanty R, Zheng Y, Li C, Gao YT, Shu XO, Zheng W. Genome-wide association study identifies breast cancer risk variant at 10q21.2: results from the Asia Breast Cancer Consortium. **Hum Mol Genet**. 2011;20(24):4991-4999. doi: 10.1093/hmg/ddr405. PubMed PMID: 21908515; PMCID: PMC3221542.
 64. Rademakers R, Baker M, Nicholson AM, Rutherford NJ, Finch N, Soto-Ortolaza A, Lash J, Wider C, Wojtas A, DeJesus-Hernandez M, Adamson J, Kouri N, Sundal C, Shuster EA, Aasly J, MacKenzie J, Roeber S, Kretschmar HA, Boeve BF, Knopman DS, Petersen RC, Cairns NJ, Ghetti B, Spina S, Garbern J, Tselis AC, Uitti R, Das P, Van Gerpen JA, Meschia JF, Levy S, Broderick DF, Graff-Radford N, Ross OA, Miller BB, Swerdlow RH, Dickson DW, Wszolek ZK. Mutations in the colony stimulating factor 1 receptor (CSF1R)

- gene cause hereditary diffuse leukoencephalopathy with spheroids. **Nat Genet.** 2011;44(2):200-205. doi: 10.1038/ng.1027. PubMed PMID: 22197934; PMCID: PMC3267847.
65. Oki NO, Motsinger-Reif AA, Antas PR, Levy S, Holland SM, Sterling TR. Novel human genetic variants associated with extrapulmonary tuberculosis: a pilot genome wide association study. **BMC Res Notes.** 2011;4:28. doi: 10.1186/1756-0500-4-28. PubMed PMID: 21281516; PMCID: PMC3041678.
 66. Beane J, Vick J, Schembri F, Anderlind C, Gower A, Campbell J, Luo L, Zhang XH, Xiao J, Alekseyev YO, Wang S, Levy S, Massion PP, Lenburg M, Spira A. Characterizing the impact of smoking and lung cancer on the airway transcriptome using RNA-Seq. **Cancer Prev Res (Phila).** 2011;4(6):803-817. doi: 10.1158/1940-6207.CAPR-11-0212. PubMed PMID: 21636547; PMCID: PMC3694393.
 67. Johansson S, Irgens H, Chudasama KK, Molnes J, Aerts J, Roque FS, Jonassen I, Levy S, Lima K, Knappskog PM, Bell GI, Molven A, Njolstad PR. Exome sequencing and genetic testing for MODY. **PLoS One.** 2012;7(5):e38050. doi: 10.1371/journal.pone.0038050. PubMed PMID: 22662265; PMCID: PMC3360646.
 68. Vilgelm A, Prasad N, Hawkins O, Levy S, Richmond A. Acquired resistance to Aurora A kinase inhibitor, Alisertib, in melanoma is associated with inhibition of tumor immune surveillance. **Pigment Cell & Melanoma Research.** 2012;25(6):894-895.
 69. Arrington CB, Bleyl SB, Matsunami N, Bonnell GD, Otterud BE, Nielsen DC, Stevens J, Levy S, Leppert MF, Bowles NE. Exome analysis of a family with pleiotropic congenital heart disease. **Circ Cardiovasc Genet.** 2012;5(2):175-182. doi: 10.1161/CIRCGENETICS.111.961797. PubMed PMID: 22337856; PMCID: PMC3329568.
 70. Neale BM, Kou Y, Liu L, Ma'ayan A, Samocha KE, Sabo A, Lin CF, Stevens C, Wang LS, Makarov V, Polak P, Yoon S, Maguire J, Crawford EL, Campbell NG, Geller ET, Valladares O, Schafer C, Liu H, Zhao T, Cai G, Lihm J, Dannenfelser R, Jabado O, Peralta Z, Nagaswamy U, Muzny D, Reid JG, Newsham I, Wu Y, Lewis L, Han Y, Voight BF, Lim E, Rossin E, Kirby A, Flannick J, Fromer M, Shakir K, Fennell T, Garimella K, Banks E, Poplin R, Gabriel S, DePristo M, Wimbish JR, Boone BE, Levy SE, Betancur C, Sunyaev S, Boerwinkle E, Buxbaum JD, Cook EH, Jr., Devlin B, Gibbs RA, Roeder K, Schellenberg GD, Sutcliffe JS, Daly MJ. Patterns and rates of exonic de novo mutations in autism spectrum disorders. **Nature.** 2012;485(7397):242-245. doi: 10.1038/nature11011. PubMed PMID: 22495311; PMCID: PMC3613847.
 71. Su Y, Vilgelm AE, Kelley MC, Hawkins OE, Liu Y, Boyd KL, Kantrow S, Splittgerber RC, Short SP, Sobolik T, Zaja-Milatovic S, Dahlman KB, Amiri KI, Jiang A, Lu P, Shyr Y, Stuart DD, Levy S, Sosman JA, Richmond A. RAF265 inhibits the growth of advanced human melanoma tumors. **Clin Cancer Res.** 2012;18(8):2184-2198. doi: 10.1158/1078-0432.CCR-11-1122. PubMed PMID: 22351689; PMCID: PMC3724517.
 72. Fiskerstrand T, Arshad N, Haukanes BI, Tronstad RR, Pham KD, Johansson S, Havik B, Tonder SL, Levy SE, Brackman D, Boman H, Biswas KH, Apold J, Hovdenak N, Visweswariah SS, Knappskog PM. Familial diarrhea syndrome caused by an activating GUCY2C mutation. **N Engl J Med.** 2012;366(17):1586-1595. doi: 10.1056/NEJMoa1110132. PubMed PMID: 22436048.
 73. Chaki M, Airik R, Ghosh AK, Giles RH, Chen R, Slaats GG, Wang H, Hurd TW, Zhou W, Cluckey A, Gee HY, Ramaswami G, Hong CJ, Hamilton BA, Cervenka I, Ganji RS, Bryja V, Arts HH, van Reeuwijk J, Oud MM, Letteboer SJ, Roepman R, Husson H, Ibraghimov-

- Beskrovnaya O, Yasunaga T, Walz G, Eley L, Sayer JA, Schermer B, Liebau MC, Benzing T, Le Corre S, Drummond I, Janssen S, Allen SJ, Natarajan S, O'Toole JF, Attanasio M, Saunier S, Antignac C, Koenekoop RK, Ren H, Lopez I, Nayir A, Stoetzel C, Dollfus H, Massoudi R, Gleeson JG, Andreoli SP, Doherty DG, Lindstrad A, Golzio C, Katsanis N, Pape L, Abboud EB, Al-Rajhi AA, Lewis RA, Omran H, Lee EY, Wang S, Sekiguchi JM, Saunders R, Johnson CA, Garner E, Vanselow K, Andersen JS, Shlomei J, Nurnberg G, Nurnberg P, Levy S, Smogorzewska A, Otto EA, Hildebrandt F. Exome capture reveals ZNF423 and CEP164 mutations, linking renal ciliopathies to DNA damage response signaling. **Cell**. 2012;150(3):533-548. doi: 10.1016/j.cell.2012.06.028. PubMed PMID: 22863007; PMCID: PMC3433835.
74. Ding D, Scott NM, Thompson EE, Chaiworapongsa T, Torres R, Billstrand C, Murray K, Dexheimer PJ, Ismail M, Kay H, Levy S, Romero R, Lindheimer MD, Nicolae DL, Ober C. Increased protein-coding mutations in the mitochondrial genome of African American women with preeclampsia. **Reprod Sci**. 2012;19(12):1343-1351. doi: 10.1177/1933719112450337. PubMed PMID: 22902742; PMCID: PMC4046444.
 75. Xu B, Ionita-Laza I, Roos JL, Boone B, Woodrick S, Sun Y, Levy S, Gogos JA, Karayiorgou M. De novo gene mutations highlight patterns of genetic and neural complexity in schizophrenia. **Nat Genet**. 2012;44(12):1365-1369. doi: 10.1038/ng.2446. PubMed PMID: 23042115; PMCID: PMC3556813.
 76. Love C, Sun Z, Jima D, Li G, Zhang J, Miles R, Richards KL, Dunphy CH, Choi WW, Srivastava G, Lugar PL, Rizzieri DA, Lagoo AS, Bernal-Mizrachi L, Mann KP, Flowers CR, Naresh KN, Evens AM, Chadburn A, Gordon LI, Czader MB, Gill JI, Hsi ED, Greenough A, Moffitt AB, McKinney M, Banerjee A, Grubor V, Levy S, Dunson DB, Dave SS. The genetic landscape of mutations in Burkitt lymphoma. **Nat Genet**. 2012;44(12):1321-1325. doi: 10.1038/ng.2468. PubMed PMID: 23143597; PMCID: PMC3674561.
 77. Zhou W, Otto EA, Cluckey A, Airik R, Hurd TW, Chaki M, Diaz K, Lach FP, Bennett GR, Gee HY, Ghosh AK, Natarajan S, Thongthip S, Veturi U, Allen SJ, Janssen S, Ramaswami G, Dixon J, Burkhalter F, Spoendlin M, Moch H, Mihatsch MJ, Verine J, Reade R, Soliman H, Godin M, Kiss D, Monga G, Mazzucco G, Amann K, Artunc F, Newland RC, Wiech T, Zschiedrich S, Huber TB, Friedl A, Slaats GG, Joles JA, Goldschmeding R, Washburn J, Giles RH, Levy S, Smogorzewska A, Hildebrandt F. FAN1 mutations cause karyomegalic interstitial nephritis, linking chronic kidney failure to defective DNA damage repair. **Nat Genet**. 2012;44(8):910-915. doi: 10.1038/ng.2347. PubMed PMID: 22772369; PMCID: PMC3412140.
 78. Nam KT, O'Neal R, Lee YS, Lee YC, Coffey RJ, Goldenring JR. Gastric tumor development in Smad3-deficient mice initiates from forestomach/glandular transition zone along the lesser curvature. **Lab Invest**. 2012;92(6):883-895. doi: 10.1038/labinvest.2012.47. PubMed PMID: 22411066; PMCID: PMC3584162.
 79. Chen XD, Xiong DH, Yang TL, Pei YF, Guo YF, Li J, Yang F, Pan F, Tan LJ, Yan H, Liu XG, Lei SF, Li X, Ning LL, Zhu XZ, Levy S, Kranzler HR, Farrer LA, Gelernter J, Recker RR, Deng HW. ANKRD7 and CYTL1 are novel risk genes for alcohol drinking behavior. **Chin Med J (Engl)**. 2012;125(6):1127-1134. PubMed PMID: 22613542; PMCID: PMC4174677.
 80. Powell AE, Wang Y, Li Y, Poulin EJ, Means AL, Washington MK, Higginbotham JN, Juchheim A, Prasad N, Levy SE, Guo Y, Shyr Y, Aronow BJ, Haigis KM, Franklin JL, Coffey RJ. The pan-ErbB negative regulator Lrig1 is an intestinal stem cell marker that

- functions as a tumor suppressor. **Cell**. 2012;149(1):146-158. doi: 10.1016/j.cell.2012.02.042. PubMed PMID: 22464327; PMCID: PMC3563328.
81. Guo Y, Cai Q, Samuels DC, Ye F, Long J, Li CI, Winther JF, Tawn EJ, Stovall M, Lahteenmaki P, Malila N, Levy S, Shaffer C, Shyr Y, Shu XO, Boice JD, Jr. The use of next generation sequencing technology to study the effect of radiation therapy on mitochondrial DNA mutation. **Mutat Res**. 2012;744(2):154-160. doi: 10.1016/j.mrgentox.2012.02.006. PubMed PMID: 22387842; PMCID: PMC3354959.
 82. Consortium EP. An integrated encyclopedia of DNA elements in the human genome. **Nature**. 2012;489(7414):57-74. doi: 10.1038/nature11247. PubMed PMID: 22955616; PMCID: PMC3439153.
 83. Buehler D, Skelton S, Corpening J, Prasad N, Levy S, Clark T, Southard-Smith E. Differential expression of Phox2b marks distinct progenitor cell populations and facilitates analysis of regulatory pathways in enteric ontogeny. **Autonomic Neuroscience: Basic and Clinical**. 2013;177(2):297.
 84. Walter RB, Laszlo GS, Alonzo TA, Gerbing RB, Levy S, Fitzgibbon MP, Gudgeon CJ, Ries RE, Harrington KH, Raimondi SC, Hirsch BA, Gamis AS, M WM, Meshinchi S. Significance of expression of ITGA5 and its splice variants in acute myeloid leukemia: a report from the Children's Oncology Group. **Am J Hematol**. 2013;88(8):694-702. doi: 10.1002/ajh.23486. PubMed PMID: 23686445; PMCID: PMC3757130.
 85. Ramirez AH, Shaffer CM, Delaney JT, Sexton DP, Levy SE, Rieder MJ, Nickerson DA, George AL, Jr., Roden DM. Novel rare variants in congenital cardiac arrhythmia genes are frequent in drug-induced torsades de pointes. **Pharmacogenomics J**. 2013;13(4):325-329. doi: 10.1038/tpj.2012.14. PubMed PMID: 22584458; PMCID: PMC3422407.
 86. Gee HY, Saisawat P, Ashraf S, Hurd TW, Vega-Warner V, Fang H, Beck BB, Gribouval O, Zhou W, Diaz KA, Natarajan S, Wiggins RC, Lovric S, Chernin G, Schoeb DS, Ovunc B, Frishberg Y, Soliman NA, Fathy HM, Goebel H, Hoefele J, Weber LT, Innis JW, Faul C, Han Z, Washburn J, Antignac C, Levy S, Otto EA, Hildebrandt F. ARHGDI mutations cause nephrotic syndrome via defective RHO GTPase signaling. **J Clin Invest**. 2013;123(8):3243-3253. doi: 10.1172/JCI69134. PubMed PMID: 23867502; PMCID: PMC3726174.
 87. Zariwala MA, Gee HY, Kurkowiak M, Al-Mutairi DA, Leigh MW, Hurd TW, Hjeij R, Dell SD, Chaki M, Dougherty GW, Adan M, Spear PC, Esteve-Rudd J, Loges NT, Rosenfeld M, Diaz KA, Olbrich H, Wolf WE, Sheridan E, Batten TF, Halbritter J, Porath JD, Kohl S, Lovric S, Hwang DY, Pittman JE, Burns KA, Ferkol TW, Sagel SD, Olivier KN, Morgan LC, Werner C, Raidt J, Pennekamp P, Sun Z, Zhou W, Airik R, Natarajan S, Allen SJ, Amirav I, Wieczorek D, Landwehr K, Nielsen K, Schwert N, Sertic J, Kohler G, Washburn J, Levy S, Fan S, Koerner-Rettberg C, Amselem S, Williams DS, Mitchell BJ, Drummond IA, Otto EA, Omran H, Knowles MR, Hildebrandt F. ZMYND10 is mutated in primary ciliary dyskinesia and interacts with LRRC6. **Am J Hum Genet**. 2013;93(2):336-345. doi: 10.1016/j.ajhg.2013.06.007. PubMed PMID: 23891469; PMCID: PMC3738827.
 88. Ashraf S, Gee HY, Woerner S, Xie LX, Vega-Warner V, Lovric S, Fang H, Song X, Cattran DC, Avila-Casado C, Paterson AD, Nitschke P, Bole-Feysot C, Cochat P, Esteve-Rudd J, Haberberger B, Allen SJ, Zhou W, Airik R, Otto EA, Barua M, Al-Hamed MH, Kari JA, Evans J, Bierzynska A, Saleem MA, Bockenbauer D, Kleta R, El Desoky S, Hacıhamdioglu DO, Gok F, Washburn J, Wiggins RC, Choi M, Lifton RP, Levy S, Han Z, Salviati L, Prokisch H, Williams DS, Pollak M, Clarke CF, Pei Y, Antignac C, Hildebrandt F. ADCK4 mutations promote steroid-resistant nephrotic syndrome through CoQ10 biosynthesis

- disruption. **J Clin Invest.** 2013;123(12):5179-5189. doi: 10.1172/JCI69000. PubMed PMID: 24270420; PMCID: PMC3859425.
89. Zhang J, Grubor V, Love CL, Banerjee A, Richards KL, Mieczkowski PA, Dunphy C, Choi W, Au WY, Srivastava G, Lugar PL, Rizzieri DA, Lagoo AS, Bernal-Mizrachi L, Mann KP, Flowers C, Naresh K, Evens A, Gordon LI, Czader M, Gill JI, Hsi ED, Liu Q, Fan A, Walsh K, Jima D, Smith LL, Johnson AJ, Byrd JC, Luftig MA, Ni T, Zhu J, Chadburn A, Levy S, Dunson D, Dave SS. Genetic heterogeneity of diffuse large B-cell lymphoma. **Proc Natl Acad Sci U S A.** 2013;110(4):1398-1403. doi: 10.1073/pnas.1205299110. PubMed PMID: 23292937; PMCID: PMC3557051.
90. Chiu IM, Morimoto ET, Goodarzi H, Liao JT, O'Keeffe S, Phatnani HP, Muratet M, Carroll MC, Levy S, Tavazoie S, Myers RM, Maniatis T. A neurodegeneration-specific gene-expression signature of acutely isolated microglia from an amyotrophic lateral sclerosis mouse model. **Cell Rep.** 2013;4(2):385-401. doi: 10.1016/j.celrep.2013.06.018. PubMed PMID: 23850290; PMCID: PMC4272581.
91. Pekow J, Dougherty U, Huang Y, Gometz E, Nathanson J, Cohen G, Levy S, Kocherginsky M, Venu N, Westerhoff M, Hart J, Noffsinger AE, Hanauer SB, Hurst RD, Fichera A, Joseph LJ, Liu Q, Bissonnette M. Gene signature distinguishes patients with chronic ulcerative colitis harboring remote neoplastic lesions. **Inflamm Bowel Dis.** 2013;19(3):461-470. doi: 10.1097/MIB.0b013e3182802bac. PubMed PMID: 23388545; PMCID: PMC3836269.
92. Franklin JL, Rankin CR, Levy S, Snoddy JR, Zhang B, Washington MK, Thomson JM, Whitehead RH, Coffey RJ. Malignant transformation of colonic epithelial cells by a colon-derived long noncoding RNA. **Biochem Biophys Res Commun.** 2013;440(1):99-104. doi: 10.1016/j.bbrc.2013.09.040. PubMed PMID: 24045012; PMCID: PMC3875348.
93. Ning MS, Kim AS, Prasad N, Levy SE, Zhang H, Andl T. Characterization of the Merkel Cell Carcinoma miRNome. **J Skin Cancer.** 2014;2014:289548. doi: 10.1155/2014/289548. PubMed PMID: 24627810; PMCID: PMC3929981.
94. Royse KE, Zhi D, Conner MG, Clodfelder-Miller B, Srinivasasainagendra V, Vaughan LK, Skibola CF, Crossman DK, Levy S, Shrestha S. Differential Gene Expression Landscape of Co-Existing Cervical Pre-Cancer Lesions Using RNA-seq. **Front Oncol.** 2014;4:339. doi: 10.3389/fonc.2014.00339. PubMed PMID: 25505737; PMCID: PMC4244708.
95. Gee HY, Otto EA, Hurd TW, Ashraf S, Chaki M, Cluckey A, Vega-Warner V, Saisawat P, Diaz KA, Fang H, Kohl S, Allen SJ, Airik R, Zhou W, Ramaswami G, Janssen S, Fu C, Innis JL, Weber S, Vester U, Davis EE, Katsanis N, Fathy HM, Jeck N, Klaus G, Nayir A, Rahim KA, Al Attrach I, Al Hassoun I, Ozturk S, Drozd D, Helmchen U, O'Toole JF, Attanasio M, Lewis RA, Nurnberg G, Nurnberg P, Washburn J, MacDonald J, Innis JW, Levy S, Hildebrandt F. Whole-exome resequencing distinguishes cystic kidney diseases from phenocopies in renal ciliopathies. **Kidney Int.** 2014;85(4):880-887. doi: 10.1038/ki.2013.450. PubMed PMID: 24257694; PMCID: PMC3972265.
96. Reinert RB, Cai Q, Hong JY, Plank JL, Aamodt K, Prasad N, Aramandla R, Dai C, Levy SE, Pozzi A, Labosky PA, Wright CV, Brissova M, Powers AC. Vascular endothelial growth factor coordinates islet innervation via vascular scaffolding. **Development.** 2014;141(7):1480-1491. doi: 10.1242/dev.098657. PubMed PMID: 24574008; PMCID: PMC3957372.
97. Vrieze SI, Malone SM, Vaidyanathan U, Kwong A, Kang HM, Zhan X, Flickinger M, Irons D, Jun G, Locke AE, Pistis G, Porcu E, Levy S, Myers RM, Oetting W, McGue M, Abecasis G, Iacono WG. In search of rare variants: preliminary results from whole genome sequencing

- of 1,325 individuals with psychophysiological endophenotypes. **Psychophysiology**. 2014;51(12):1309-1320. doi: 10.1111/psyp.12350. PubMed PMID: 25387710; PMCID: PMC4231480.
98. Gee HY, Ashraf S, Wan X, Vega-Warner V, Esteve-Rudd J, Lovric S, Fang H, Hurd TW, Sadowski CE, Allen SJ, Otto EA, Korkmaz E, Washburn J, Levy S, Williams DS, Bakkaloglu SA, Zolotnitskaya A, Ozaltin F, Zhou W, Hildebrandt F. Mutations in EMP2 cause childhood-onset nephrotic syndrome. **Am J Hum Genet**. 2014;94(6):884-890. doi: 10.1016/j.ajhg.2014.04.010. PubMed PMID: 24814193; PMCID: PMC4121470.
 99. Brissova M, Aamodt K, Brahmachary P, Prasad N, Hong JY, Dai C, Mellati M, Shostak A, Poffenberger G, Aramandla R, Levy SE, Powers AC. Islet microenvironment, modulated by vascular endothelial growth factor-A signaling, promotes beta cell regeneration. **Cell Metab**. 2014;19(3):498-511. doi: 10.1016/j.cmet.2014.02.001. PubMed PMID: 24561261; PMCID: PMC4012856.
 100. Zhang J, Jima D, Moffitt AB, Liu Q, Czader M, Hsi ED, Fedoriw Y, Dunphy CH, Richards KL, Gill JI, Sun Z, Love C, Scotland P, Lock E, Levy S, Hsu DS, Dunson D, Dave SS. The genomic landscape of mantle cell lymphoma is related to the epigenetically determined chromatin state of normal B cells. **Blood**. 2014;123(19):2988-2996. doi: 10.1182/blood-2013-07-517177. PubMed PMID: 24682267; PMCID: PMC4014841.
 101. Campbell AG, Schwientek P, Vishnivetskaya T, Woyke T, Levy S, Beall CJ, Griffen A, Leys E, Podar M. Diversity and genomic insights into the uncultured Chloroflexi from the human microbiota. **Environ Microbiol**. 2014;16(9):2635-2643. doi: 10.1111/1462-2920.12461. PubMed PMID: 24738594; PMCID: PMC4149597.
 102. Li S, Tighe SW, Nicolet CM, Grove D, Levy S, Farmerie W, Viale A, Wright C, Schweitzer PA, Gao Y, Kim D, Boland J, Hicks B, Kim R, Chhangawala S, Jafari N, Raghavachari N, Gandara J, Garcia-Reyero N, Hendrickson C, Roberson D, Rosenfeld J, Smith T, Underwood JG, Wang M, Zumbo P, Baldwin DA, Grills GS, Mason CE. Multi-platform assessment of transcriptome profiling using RNA-seq in the ABRF next-generation sequencing study. **Nat Biotechnol**. 2014;32(9):915-925. doi: 10.1038/nbt.2972. PubMed PMID: 25150835; PMCID: PMC4167418.
 103. Picard M, Zhang J, Hancock S, Derbeneva O, Golhar R, Golik P, O'Hearn S, Levy S, Potluri P, Lvova M, Davila A, Lin CS, Perin JC, Rappaport EF, Hakonarson H, Trounce IA, Procaccio V, Wallace DC. Progressive increase in mtDNA 3243A>G heteroplasmy causes abrupt transcriptional reprogramming. **Proc Natl Acad Sci U S A**. 2014;111(38):E4033-4042. doi: 10.1073/pnas.1414028111. PubMed PMID: 25192935; PMCID: PMC4183335.
 104. Vilgelm A, Johnson A, Prasad N, Yang J, Chen S-c, Ayers G, Pawlikowski J, Raman D, Sosman J, Kelley M. Therapy-induced senescence promotes a tumor suppressive immune microenvironment via Nfkb-mediated induction of Ccl5. **Pigment Cell & Melanoma Research**. 2015;28(6):820.
 105. Hsu CH, Nguyen C, Yan C, Ries RE, Chen QR, Hu Y, Ostronoff F, Stirewalt DL, Komatsoulis G, Levy S, Meerzaman D, Meshinchi S. Transcriptome Profiling of Pediatric Core Binding Factor AML. **PLoS One**. 2015;10(9):e0138782. doi: 10.1371/journal.pone.0138782. PubMed PMID: 26397705; PMCID: PMC4580636.
 106. Hoek KL, Samir P, Howard LM, Niu X, Prasad N, Galassie A, Liu Q, Allos TM, Floyd KA, Guo Y, Shyr Y, Levy SE, Joyce S, Edwards KM, Link AJ. A cell-based systems biology assessment of human blood to monitor immune responses after influenza vaccination.

- PLoS One.** 2015;10(2):e0118528. doi: 10.1371/journal.pone.0118528. PubMed PMID: 25706537; PMCID: PMC4338067.
107. Afshinnnekoo E, Meydan C, Chowdhury S, Jaroudi D, Boyer C, Bernstein N, Maritz JM, Reeves D, Gandara J, Chhangawala S. Modern methods for delineating metagenomic complexity. **Cell systems.** 2015;1(1):6-7.
 108. Strong KA, May T, Levy SA. In sickness and in health: context matters when considering potential benefits and risks of genome-wide sequencing. **Genet Med.** 2015;17(8):681-682. doi: 10.1038/gim.2015.85. PubMed PMID: 26240975.
 109. Zhi D, Shendre A, Scherzer R, Irvin MR, Perry RT, Levy S, Arnett DK, Grunfeld C, Shrestha S. Deep sequencing of RYR3 gene identifies rare and common variants associated with increased carotid intima-media thickness (cIMT) in HIV-infected individuals. **J Hum Genet.** 2015;60(2):63-67. doi: 10.1038/jhg.2014.104. PubMed PMID: 25500725.
 110. Ebarasi L, Ashraf S, Bierzynska A, Gee HY, McCarthy HJ, Lovric S, Sadowski CE, Pabst W, Vega-Warner V, Fang H, Koziell A, Simpson MA, Dursun I, Serdaroglu E, Levy S, Saleem MA, Hildebrandt F, Majumdar A. Defects of CRB2 cause steroid-resistant nephrotic syndrome. **Am J Hum Genet.** 2015;96(1):153-161. doi: 10.1016/j.ajhg.2014.11.014. PubMed PMID: 25557779; PMCID: PMC4289689.
 111. Cha DJ, Franklin JL, Dou Y, Liu Q, Higginbotham JN, Demory Beckler M, Weaver AM, Vickers K, Prasad N, Levy S, Zhang B, Coffey RJ, Patton JG. KRAS-dependent sorting of miRNA to exosomes. **Elife.** 2015;4:e07197. doi: 10.7554/eLife.07197. PubMed PMID: 26132860; PMCID: PMC4510696.
 112. Afshinnnekoo E, Meydan C, Chowdhury S, Jaroudi D, Boyer C, Bernstein N, Maritz JM, Reeves D, Gandara J, Chhangawala S, Ahsanuddin S, Simmons A, Nessel T, Sundares B, Pereira E, Jorgensen E, Kolokotronis SO, Kirchberger N, Garcia I, Gandara D, Dhanraj S, Nawrin T, Saletore Y, Alexander N, Vijay P, Henaff EM, Zumbo P, Walsh M, O'Mullan GD, Tighe S, Dudley JT, Dunaif A, Ennis S, O'Halloran E, Magalhaes TR, Boone B, Jones AL, Muth TR, Paolantonio KS, Alter E, Schadt EE, Garbarino J, Prill RJ, Carlton JM, Levy S, Mason CE. Geospatial Resolution of Human and Bacterial Diversity with City-Scale Metagenomics. **Cell Syst.** 2015;1(1):72-87. doi: 10.1016/j.cels.2015.01.001. PubMed PMID: 26594662; PMCID: PMC4651444.
 113. Gee HY, Zhang F, Ashraf S, Kohl S, Sadowski CE, Vega-Warner V, Zhou W, Lovric S, Fang H, Nettleton M, Zhu JY, Hoefele J, Weber LT, Podracka L, Boor A, Fehrenbach H, Innis JW, Washburn J, Levy S, Lifton RP, Otto EA, Han Z, Hildebrandt F. KANK deficiency leads to podocyte dysfunction and nephrotic syndrome. **J Clin Invest.** 2015;125(6):2375-2384. doi: 10.1172/JCI79504. PubMed PMID: 25961457; PMCID: PMC4497755.
 114. Cirulli ET, Lasseigne BN, Petrovski S, Sapp PC, Dion PA, Leblond CS, Couthouis J, Lu YF, Wang Q, Krueger BJ, Ren Z, Keebler J, Han Y, Levy SE, Boone BE, Wimbish JR, Waite LL, Jones AL, Carulli JP, Day-Williams AG, Staropoli JF, Xin WW, Chesi A, Raphael AR, McKenna-Yasek D, Cady J, Vianney de Jong JM, Kenna KP, Smith BN, Topp S, Miller J, Gkazi A, Consortium FS, Al-Chalabi A, van den Berg LH, Veldink J, Silani V, Ticozzi N, Shaw CE, Baloh RH, Appel S, Simpson E, Lagier-Tourenne C, Pulst SM, Gibson S, Trojanowski JQ, Elman L, McCluskey L, Grossman M, Shneider NA, Chung WK, Ravits JM, Glass JD, Sims KB, Van Deerlin VM, Maniatis T, Hayes SD, Ordureau A, Swarup S, Landers J, Baas F, Allen AS, Bedlack RS, Harper JW, Gitler AD, Rouleau GA, Brown R, Harms MB, Cooper GM, Harris T, Myers RM, Goldstein DB. Exome sequencing in amyotrophic lateral sclerosis identifies risk genes and pathways. **Science.**

- 2015;347(6229):1436-1441. doi: 10.1126/science.aaa3650. PubMed PMID: 25700176; PMCID: PMC4437632.
115. Zea L, Prasad N, Levy SE, Stodieck L, Jones A, Shrestha S, Klaus D. A Molecular Genetic Basis Explaining Altered Bacterial Behavior in Space. **PLoS One**. 2016;11(11):e0164359. doi: 10.1371/journal.pone.0164359. PubMed PMID: 27806055; PMCID: PMC5091764.
116. McGrath K, McGrath L, Gray A, Osuolale O, Segata N, Fillo S, Iraola G, Zhou Y, Chang Y, Li Y. The Metagenomics and Metadesign of the Subways and Urban Biomes (MetaSUB) International Consortium Inaugural Meeting Report (vol 4, 24, 2016). **MICROBIOME**. 2016;4.
117. Levy SE, Myers RM. Advancements in next-generation sequencing. **Annual review of genomics and human genetics**. 2016;17:95-115.
118. Graham HT, Rotroff DM, Marvel SW, Buse JB, Havener TM, Wilson AG, Wagner MJ, Motsinger-Reif AA, Investigators AA. Incorporating Concomitant Medications into Genome-Wide Analyses for the Study of Complex Disease and Drug Response. **Frontiers in genetics**. 2016;7.
119. Alam SG, Zhang Q, Prasad N, Li Y, Chamala S, Kuchibhotla R, Kc B, Aggarwal V, Shrestha S, Jones AL, Levy SE, Roux KJ, Nickerson JA, Lele TP. The mammalian LINC complex regulates genome transcriptional responses to substrate rigidity. **Sci Rep**. 2016;6:38063. doi: 10.1038/srep38063. PubMed PMID: 27905489; PMCID: PMC5131312.
120. Grimes JA, Prasad N, Levy S, Cattley R, Lindley S, Boothe HW, Henderson RA, Smith BF. A comparison of microRNA expression profiles from splenic hemangiosarcoma, splenic nodular hyperplasia, and normal spleens of dogs. **BMC Vet Res**. 2016;12(1):272. doi: 10.1186/s12917-016-0903-5. PubMed PMID: 27912752; PMCID: PMC5135805.
121. Rahman KM, Camp ME, Prasad N, McNeel AK, Levy SE, Bartol FF, Bagnell CA. Age and Nursing Affect the Neonatal Porcine Uterine Transcriptome. **Biol Reprod**. 2016;94(2):46. doi: 10.1095/biolreprod.115.136150. PubMed PMID: 26632611.
122. Vilgelm AE, Johnson CA, Prasad N, Yang J, Chen SC, Ayers GD, Pawlikowski JS, Raman D, Sosman JA, Kelley M, Ecsedy JA, Shyr Y, Levy SE, Richmond A. Connecting the Dots: Therapy-Induced Senescence and a Tumor-Suppressive Immune Microenvironment. **J Natl Cancer Inst**. 2016;108(6):djv406. doi: 10.1093/jnci/djv406. PubMed PMID: 26719346; PMCID: PMC4849355.
123. Goes FS, Pirooznia M, Parla JS, Kramer M, Ghiban E, Mavruk S, Chen YC, Monson ET, Willour VL, Karchin R, Flickinger M, Locke AE, Levy SE, Scott LJ, Boehnke M, Stahl E, Moran JL, Hultman CM, Landen M, Purcell SM, Sklar P, Zandi PP, McCombie WR, Potash JB. Exome Sequencing of Familial Bipolar Disorder. **JAMA Psychiatry**. 2016;73(6):590-597. doi: 10.1001/jamapsychiatry.2016.0251. PubMed PMID: 27120077.
124. Dou Y, Cha DJ, Franklin JL, Higginbotham JN, Jeppesen DK, Weaver AM, Prasad N, Levy S, Coffey RJ, Patton JG, Zhang B. Circular RNAs are down-regulated in KRAS mutant colon cancer cells and can be transferred to exosomes. **Sci Rep**. 2016;6:37982. doi: 10.1038/srep37982. PubMed PMID: 27892494; PMCID: PMC5125100.
125. McCarthy S, Das S, Kretzschmar W, Delaneau O, Wood AR, Teumer A, Kang HM, Fuchsberger C, Danecek P, Sharp K, Luo Y, Sidore C, Kwong A, Timpson N, Koskinen S, Vrieze S, Scott LJ, Zhang H, Mahajan A, Veldink J, Peters U, Pato C, van Duijn CM, Gillies CE, Gandin I, Mezzavilla M, Gilly A, Cocca M, Traglia M, Angius A, Barrett JC, Boomsma D, Branham K, Breen G, Brummett CM, Busonero F, Campbell H, Chan A, Chen S, Chew E, Collins FS, Corbin LJ, Smith GD, Dedoussis G, Dorr M, Farmaki AE, Ferrucci L, Forer L,

- Fraser RM, Gabriel S, Levy S, Groop L, Harrison T, Hattersley A, Holmen OL, Hveem K, Kretzler M, Lee JC, McGue M, Meitinger T, Melzer D, Min JL, Mohlke KL, Vincent JB, Nauck M, Nickerson D, Palotie A, Pato M, Pirastu N, McInnis M, Richards JB, Sala C, Salomaa V, Schlessinger D, Schoenherr S, Slagboom PE, Small K, Spector T, Stambolian D, Tuke M, Tuomilehto J, Van den Berg LH, Van Rheenen W, Volker U, Wijmenga C, Toniolo D, Zeggini E, Gasparini P, Sampson MG, Wilson JF, Frayling T, de Bakker PI, Swertz MA, McCarroll S, Kooperberg C, Dekker A, Altshuler D, Willer C, Iacono W, Ripatti S, Soranzo N, Walter K, Swaroop A, Cucca F, Anderson CA, Myers RM, Boehnke M, McCarthy MI, Durbin R, Haplotype Reference C. A reference panel of 64,976 haplotypes for genotype imputation. **Nat Genet.** 2016;48(10):1279-1283. doi: 10.1038/ng.3643. PubMed PMID: 27548312; PMCID: PMC5388176.
126. Das S, Forer L, Schonherr S, Sidore C, Locke AE, Kwong A, Vrieze SI, Chew EY, Levy S, McGue M, Schlessinger D, Stambolian D, Loh PR, Iacono WG, Swaroop A, Scott LJ, Cucca F, Kronenberg F, Boehnke M, Abecasis GR, Fuchsberger C. Next-generation genotype imputation service and methods. **Nat Genet.** 2016;48(10):1284-1287. doi: 10.1038/ng.3656. PubMed PMID: 27571263; PMCID: PMC5157836.
 127. Mason C, McIntyre A, Ounit R, Afshinnekoo E, Prill R, Henaff E, Alexander N, Minot S, Danko D, Foox J. Comprehensive Benchmarking and Ensemble Approaches for Metagenomic Classifiers. **bioRxiv.** 2017:156919.
 128. Howard LM, Hoek KL, Goll JB, Samir P, Galassie A, Allos TM, Niu X, Gordy LE, Creech CB, Prasad N, Jensen TL, Hill H, Levy SE, Joyce S, Link AJ, Edwards KM. Cell-Based Systems Biology Analysis of Human AS03-Adjuvanted H5N1 Avian Influenza Vaccine Responses: A Phase I Randomized Controlled Trial. **PLoS One.** 2017;12(1):e0167488. doi: 10.1371/journal.pone.0167488. PubMed PMID: 28099485; PMCID: PMC5242433.
 129. Carlson J, Scott LJ, Locke AE, Flickinger M, Levy S, Myers RM, Boehnke M, Kang HM, Li JZ, Zöllner S. Extremely rare variants reveal patterns of germline mutation rate heterogeneity in humans. **bioRxiv.** 2017:108290.
 130. Johansson BB, Irgens HU, Molnes J, Sztromwasser P, Aukrust I, Juliusson PB, Sovik O, Levy S, Skriverhaug T, Joner G, Molven A, Johansson S, Njolstad PR. Targeted next-generation sequencing reveals MODY in up to 6.5% of antibody-negative diabetes cases listed in the Norwegian Childhood Diabetes Registry. **Diabetologia.** 2017;60(4):625-635. doi: 10.1007/s00125-016-4167-1. PubMed PMID: 27913849.
 131. Mason CE, Afshinnekoo E, Tighe S, Wu S, Levy S. International Standards for Genomes, Transcriptomes, and Metagenomes. **J Biomol Tech.** 2017;28(1):8-18. doi: 10.7171/jbt.17-2801-006. PubMed PMID: 28337071; PMCID: PMC5359768.
 132. McKinney M, Moffitt AB, Gaulard P, Travert M, De Leval L, Nicolae A, Raffeld M, Jaffe ES, Pittaluga S, Xi L, Heavican T, Iqbal J, Belhadj K, Delfau-Larue MH, Fataccioli V, Czader MB, Lossos IS, Chapman-Fredricks JR, Richards KL, Fedoriw Y, Ondrejka SL, Hsi ED, Low L, Weisenburger D, Chan WC, Mehta-Shah N, Horwitz S, Bernal-Mizrachi L, Flowers CR, Beaven AW, Parihar M, Baseggio L, Parrens M, Moreau A, Sujobert P, Pilichowska M, Evens AM, Chadburn A, Au-Yeung RK, Srivastava G, Choi WW, Goodlad JR, Aurer I, Basic-Kinda S, Gascoyne RD, Davis NS, Li G, Zhang J, Rajagopalan D, Reddy A, Love C, Levy S, Zhuang Y, Datta J, Dunson DB, Dave SS. The Genetic Basis of Hepatosplenic T-cell Lymphoma. **Cancer Discov.** 2017;7(4):369-379. doi: 10.1158/2159-8290.CD-16-0330. PubMed PMID: 28122867; PMCID: PMC5402251.
 133. Tighe S, Afshinnekoo E, Rock TM, McGrath K, Alexander N, McIntyre A, Ahsanuddin S, Bezdán D, Green SJ, Joye S, Stewart Johnson S, Baldwin DA, Bivens N, Ajami N,

- Carmical JR, Herriott IC, Colwell R, Donia M, Foox J, Greenfield N, Hunter T, Hoffman J, Hyman J, Jorgensen E, Krawczyk D, Lee J, Levy S, Garcia-Reyero N, Settles M, Thomas K, Gomez F, Schriml L, Kyrpides N, Zaikova E, Penterman J, Mason CE. Genomic Methods and Microbiological Technologies for Profiling Novel and Extreme Environments for the Extreme Microbiome Project (XMP). **J Biomol Tech.** 2017;28(1):31-39. doi: 10.7171/jbt.17-2801-004. PubMed PMID: 28337070; PMCID: PMC5345951.
134. Gosline SJ, Weinberg H, Knight P, Yu T, Guo X, Prasad N, Jones A, Shrestha S, Boone B, Levy SE, La Rosa S, Guinney J, Bakker A. A high-throughput molecular data resource for cutaneous neurofibromas. **Sci Data.** 2017;4:170045. doi: 10.1038/sdata.2017.45. PubMed PMID: 28398289; PMCID: PMC5387919.
 135. Chao HT, Davids M, Burke E, Pappas JG, Rosenfeld JA, McCarty AJ, Davis T, Wolfe L, Toro C, Tifft C, Xia F, Stong N, Johnson TK, Warr CG, Undiagnosed Diseases N, Yamamoto S, Adams DR, Markello TC, Gahl WA, Bellen HJ, Wangler MF, Malicdan MC. A Syndromic Neurodevelopmental Disorder Caused by De Novo Variants in EBF3. **Am J Hum Genet.** 2017;100(1):128-137. doi: 10.1016/j.ajhg.2016.11.018. PubMed PMID: 28017372; PMCID: PMC5223093.
 136. McDaniel JM, Varley KE, Gertz J, Savic DS, Roberts BS, Bailey SK, Shevde LA, Ramaker RC, Lasseigne BN, Kirby MK, Newberry KM, Partridge EC, Jones AL, Boone B, Levy SE, Oliver PG, Sexton KC, Grizzle WE, Forero A, Buchsbaum DJ, Cooper SJ, Myers RM. Genomic regulation of invasion by STAT3 in triple negative breast cancer. **Oncotarget.** 2017;8(5):8226-8238. doi: 10.18632/oncotarget.14153. PubMed PMID: 28030809; PMCID: PMC5352396.
 137. Dean ED, Li M, Prasad N, Wisniewski SN, Von Deylen A, Spaeth J, Maddison L, Botros A, Sedgeman LR, Bozadjieva N, Ilkayeva O, Coldren A, Poffenberger G, Shostak A, Semich MC, Aamodt KI, Phillips N, Yan H, Bernal-Mizrachi E, Corbin JD, Vickers KC, Levy SE, Dai C, Newgard C, Gu W, Stein R, Chen W, Powers AC. Interrupted Glucagon Signaling Reveals Hepatic alpha Cell Axis and Role for L-Glutamine in alpha Cell Proliferation. **Cell Metab.** 2017;25(6):1362-1373 e1365. doi: 10.1016/j.cmet.2017.05.011. PubMed PMID: 28591638.
 138. Steffen MM, Davis TW, McKay RML, Bullerjahn GS, Krausfeldt LE, Stough JMA, Neitzey ML, Gilbert NE, Boyer GL, Johengen TH, Gossiaux DC, Burtner AM, Palladino D, Rowe MD, Dick GJ, Meyer KA, Levy S, Boone BE, Stumpf RP, Wynne TT, Zimba PV, Gutierrez D, Wilhelm SW. Ecophysiological Examination of the Lake Erie Microcystis Bloom in 2014: Linkages between Biology and the Water Supply Shutdown of Toledo, OH. **Environ Sci Technol.** 2017;51(12):6745-6755. doi: 10.1021/acs.est.7b00856. PubMed PMID: 28535339.
 139. Luo W, Galvan DL, Woodard LE, Dorset D, Levy S, Wilson MH. Comparative analysis of chimeric ZFP-, TALE- and Cas9-piggyBac transposases for integration into a single locus in human cells. **Nucleic Acids Res.** 2017. doi: 10.1093/nar/gkx572. PubMed PMID: 28666380.
 140. Moffitt AB, Ondrejka SL, McKinney M, Rempel RE, Goodlad JR, Teh CH, Leppa S, Mannisto S, Kovanen PE, Tse E, Au-Yeung RKH, Kwong YL, Srivastava G, Iqbal J, Yu J, Naresh K, Villa D, Gascoyne RD, Said J, Czader MB, Chadburn A, Richards KL, Rajagopalan D, Davis NS, Smith EC, Palus BC, Tzeng TJ, Healy JA, Lugar PL, Datta J, Love C, Levy S, Dunson DB, Zhuang Y, Hsi ED, Dave SS. Enteropathy-associated T cell lymphoma subtypes are characterized by loss of function of SETD2. **J Exp Med.**

- 2017;214(5):1371-1386. doi: 10.1084/jem.20160894. PubMed PMID: 28424246; PMCID: PMC5413324.
141. Dai C, Hang Y, Shostak A, Poffenberger G, Hart N, Prasad N, Phillips N, Levy SE, Greiner DL, Shultz LD, Bottino R, Kim SK, Powers AC. Age-dependent human beta cell proliferation induced by glucagon-like peptide 1 and calcineurin signaling. **J Clin Invest.** 2017;127(10):3835-3844. doi: 10.1172/JCI91761. PubMed PMID: 28920919; PMCID: PMC5617654.
142. Reddy A, Zhang J, Davis NS, Moffitt AB, Love CL, Waldrop A, Leppa S, Pasanen A, Meriranta L, Karjalainen-Lindsberg ML, Norgaard P, Pedersen M, Gang AO, Hogdall E, Heavican TB, Lone W, Iqbal J, Qin Q, Li G, Kim SY, Healy J, Richards KL, Fedoriw Y, Bernal-Mizrachi L, Koff JL, Staton AD, Flowers CR, Paltiel O, Goldschmidt N, Calaminici M, Clear A, Gribben J, Nguyen E, Czader MB, Ondrejka SL, Collie A, Hsi ED, Tse E, Au-Yeung RKH, Kwong YL, Srivastava G, Choi WWL, Evens AM, Pilichowska M, Sengar M, Reddy N, Li S, Chadburn A, Gordon LI, Jaffe ES, Levy S, Rempel R, Tzeng T, Happ LE, Dave T, Rajagopalan D, Datta J, Dunson DB, Dave SS. Genetic and Functional Drivers of Diffuse Large B Cell Lymphoma. **Cell.** 2017;171(2):481-494 e415. doi: 10.1016/j.cell.2017.09.027. PubMed PMID: 28985567; PMCID: PMC5659841.
143. McIntyre ABR, Ounit R, Afshinnkoo E, Prill RJ, Henaff E, Alexander N, Minot SS, Danko D, Foox J, Ahsanuddin S, Tighe S, Hasan NA, Subramanian P, Moffat K, Levy S, Lonardi S, Greenfield N, Colwell RR, Rosen GL, Mason CE. Comprehensive benchmarking and ensemble approaches for metagenomic classifiers. **Genome Biol.** 2017;18(1):182. doi: 10.1186/s13059-017-1299-7. PubMed PMID: 28934964; PMCID: PMC5609029.
144. O'Hara NB, Reed HJ, Afshinnkoo E, Harvin D, Caplan N, Rosen G, Frye B, Woloszynek S, Ounit R, Levy S, Butler E, Mason CE. Metagenomic characterization of ambulances across the USA. **Microbiome.** 2017;5(1):125. doi: 10.1186/s40168-017-0339-6. PubMed PMID: 28938903; PMCID: PMC5610413.
145. Aunins TR, Erickson KE, Prasad N, Levy SE, Jones A, Shrestha S, Mastracchio R, Stodieck L, Klaus D, Zea L, Chatterjee A. Spaceflight Modifies Escherichia coli Gene Expression in Response to Antibiotic Exposure and Reveals Role of Oxidative Stress Response. **Front Microbiol.** 2018;9:310. doi: 10.3389/fmicb.2018.00310. PubMed PMID: 29615983; PMCID: PMC5865062.
146. Thompson ML, Finnila CR, Bowling KM, Brothers KB, Neu MB, Amaral MD, Hiatt SM, East KM, Gray DE, Lawlor JMJ, Kelley WV, Lose EJ, Rich CA, Simmons S, Levy SE, Myers RM, Barsh GS, Bebin EM, Cooper GM. Genomic sequencing identifies secondary findings in a cohort of parent study participants. **Genet Med.** 2018. doi: 10.1038/gim.2018.53. PubMed PMID: 29790872.
147. Marcogliese PC, Shashi V, Spillmann RC, Stong N, Rosenfeld JA, Koenig MK, Martinez-Agosto JA, Herzog M, Chen AH, Dickson PI, Lin HJ, Vera MU, Salamon N, Graham JM, Jr., Ortiz D, Infante E, Steyaert W, Dermaut B, Poppe B, Chung HL, Zuo Z, Lee PT, Kanca O, Xia F, Yang Y, Smith EC, Jasien J, Kansagra S, Spiridigliozzi G, El-Dairi M, Lark R, Riley K, Koeberl DD, Golden-Grant K, Program for Undiagnosed D, Undiagnosed Diseases N, Yamamoto S, Wangler MF, Mirzaa G, Hemelsoet D, Lee B, Nelson SF, Goldstein DB, Bellen HJ, Pena LDM. IRF2BPL Is Associated with Neurological Phenotypes. **Am J Hum Genet.** 2018;103(2):245-260. doi: 10.1016/j.ajhg.2018.07.006. PubMed PMID: 30057031; PMCID: PMC6081494.
148. Schlegel C, Lapierre LA, Weis VG, Williams JA, Kaji I, Pinzon-Guzman C, Prasad N, Boone B, Jones A, Correa H, Levy SE, Han X, Wang M, Thomsen K, Acra S, Goldenring JR.

- Reversible deficits in apical transporter trafficking associated with deficiency in diacylglycerol acyltransferase. **Traffic**. 2018. doi: 10.1111/tra.12608. PubMed PMID: 30095213.
149. Schlegel C, Lapierre LA, Weis VG, Williams JA, Kaji I, Pinzon-Guzman C, Prasad N, Boone B, Jones A, Correa H, Levy SE, Han X, Wang M, Thomsen K, Acra S, Goldenring JR. Reversible deficits in apical transporter trafficking associated with DGAT1 deficiency. **Traffic**. 2018. doi: 10.1111/tra.12608. PubMed PMID: 30095213.
 150. Keele GR, Prokop JW, He H, Holl K, Littrell J, Deal A, Francic S, Cui L, Gatti DM, Broman KW, Tschannen M, Tsaih SW, Zagloul M, Kim Y, Baur B, Fox J, Robinson M, Levy S, Flister MJ, Mott R, Valdar W, Solberg Woods LC. Genetic Fine-Mapping and Identification of Candidate Genes and Variants for Adiposity Traits in Outbred Rats. **Obesity (Silver Spring)**. 2018;26(1):213-222. doi: 10.1002/oby.22075. PubMed PMID: 29193816; PMCID: PMC5740008.
 151. Hiatt SM, Amaral MD, Bowling KM, Finnila CR, Thompson ML, Gray DE, Lawlor JMJ, Cochran JN, Bebin EM, Brothers KB, East KM, Kelley WV, Lamb NE, Levy SE, Lose EJ, Neu MB, Rich CA, Simmons S, Myers RM, Barsh GS, Cooper GM. Systematic reanalysis of genomic data improves quality of variant interpretation. **Clin Genet**. 2018;94(1):174-178. doi: 10.1111/cge.13259. PubMed PMID: 29652076; PMCID: PMC5995667.
 152. Weiss H, Hertzberg VS, Dupont C, Espinoza JL, Levy S, Nelson K, Norris S, FlyHealthy Research T. The Airplane Cabin Microbiome. **Microb Ecol**. 2018. doi: 10.1007/s00248-018-1191-3. PubMed PMID: 29876609.
 153. Bipolar D, Schizophrenia Working Group of the Psychiatric Genomics Consortium. Electronic address drve, Bipolar D, Schizophrenia Working Group of the Psychiatric Genomics C. Genomic Dissection of Bipolar Disorder and Schizophrenia, Including 28 Subphenotypes. **Cell**. 2018;173(7):1705-1715 e1716. doi: 10.1016/j.cell.2018.05.046. PubMed PMID: 29906448.
 154. Shashi V, Schoch K, Spillmann R, Cope H, Tan QK, Walley N, Pena L, McConkie-Rosell A, Jiang YH, Stong N, Need AC, Goldstein DB, Undiagnosed Diseases N. A comprehensive iterative approach is highly effective in diagnosing individuals who are exome negative. **Genet Med**. 2018. doi: 10.1038/s41436-018-0044-2. PubMed PMID: 29907797.
 155. Olahova M, Yoon WH, Thompson K, Jangam S, Fernandez L, Davidson JM, Kyle JE, Grove ME, Fisk DG, Kohler JN, Holmes M, Dries AM, Huang Y, Zhao C, Contrepois K, Zappala Z, Fresard L, Waggott D, Zink EM, Kim YM, Heyman HM, Stratton KG, Webb-Robertson BM, Undiagnosed Diseases N, Snyder M, Merker JD, Montgomery SB, Fisher PG, Feichtinger RG, Mayr JA, Hall J, Barbosa IA, Simpson MA, Deshpande C, Waters KM, Koeller DM, Metz TO, Morris AA, Schelley S, Cowan T, Friederich MW, McFarland R, Van Hove JKL, Enns GM, Yamamoto S, Ashley EA, Wangler MF, Taylor RW, Bellen HJ, Bernstein JA, Wheeler MT. Biallelic Mutations in ATP5F1D, which Encodes a Subunit of ATP Synthase, Cause a Metabolic Disorder. **Am J Hum Genet**. 2018;102(3):494-504. doi: 10.1016/j.ajhg.2018.01.020. PubMed PMID: 29478781.
 156. Brissova M, Haliyur R, Saunders D, Shrestha S, Dai C, Blodgett DM, Bottino R, Campbell-Thompson M, Aramandla R, Poffenberger G, Lindner J, Pan FC, von Herrath MG, Greiner DL, Shultz LD, Sanyoura M, Philipson LH, Atkinson M, Harlan DM, Levy SE, Prasad N, Stein R, Powers AC. alpha Cell Function and Gene Expression Are Compromised in Type 1 Diabetes. **Cell Rep**. 2018;22(10):2667-2676. doi: 10.1016/j.celrep.2018.02.032. PubMed PMID: 29514095.

157. Nicolas A, Kenna KP, Renton AE, Ticozzi N, Faghri F, Chia R, Dominov JA, Kenna BJ, Nalls MA, Keagle P, Rivera AM, van Rheenen W, Murphy NA, van Vugt J, Geiger JT, Van der Spek RA, Pliner HA, Shankaracharya, Smith BN, Marangi G, Topp SD, Abramzon Y, Gkazi AS, Eicher JD, Kenna A, Consortium I, Mora G, Calvo A, Mazzini L, Riva N, Mandrioli J, Caponnetto C, Battistini S, Volanti P, La Bella V, Conforti FL, Borghero G, Messina S, Simone IL, Trojsi F, Salvi F, Logullo FO, D'Alfonso S, Corrado L, Capasso M, Ferrucci L, Genomic Translation for ALSCC, Moreno CAM, Kamalakaran S, Goldstein DB, Consortium ALSS, Gitler AD, Harris T, Myers RM, Consortium NA, Phatnani H, Musunuri RL, Evani US, Abhyankar A, Zody MC, Answer ALSF, Kaye J, Finkbeiner S, Wyman SK, LeNail A, Lima L, Fraenkel E, Svendsen CN, Thompson LM, Van Eyk JE, Berry JD, Miller TM, Kolb SJ, Cudkowicz M, Baxi E, Clinical Research in ALS, Related Disorders for Therapeutic Development C, Benatar M, Taylor JP, Rampersaud E, Wu G, Wu J, Consortium S, Lauria G, Verde F, Fogh I, Tiloca C, Comi GP, Soraru G, Cereda C, French ALSC, Corcia P, Laaksovirta H, Myllykangas L, Jansson L, Valori M, Ealing J, Hamdalla H, Rollinson S, Pickering-Brown S, Orrell RW, Sidle KC, Malaspina A, Hardy J, Singleton AB, Johnson JO, Arepalli S, Sapp PC, McKenna-Yasek D, Polak M, Asress S, Al-Sarraj S, King A, Troakes C, Vance C, de Belleruche J, Baas F, Ten Asbroek A, Munoz-Blanco JL, Hernandez DG, Ding J, Gibbs JR, Scholz SW, Floeter MK, Campbell RH, Landi F, Bowser R, Pulst SM, Ravits JM, MacGowan DJL, Kirby J, Pioro EP, Pamphlett R, Broach J, Gerhard G, Dunckley TL, Brady CB, Kowall NW, Troncoso JC, Le Ber I, Mouzat K, Lumbroso S, Heiman-Patterson TD, Kamel F, Van Den Bosch L, Baloh RH, Strom TM, Meitinger T, Shatunov A, Van Eijk KR, de Carvalho M, Kooyman M, Middelkoop B, Moisse M, McLaughlin RL, Van Es MA, Weber M, Boylan KB, Van Blitterswijk M, Rademakers R, Morrison KE, Basak AN, Mora JS, Drory VE, Shaw PJ, Turner MR, Talbot K, Hardiman O, Williams KL, Fifita JA, Nicholson GA, Blair IP, Rouleau GA, Esteban-Perez J, Garcia-Redondo A, Al-Chalabi A, Project Min EALSSC, Rogaeva E, Zinman L, Ostrow LW, Maragakis NJ, Rothstein JD, Simmons Z, Cooper-Knock J, Brice A, Goutman SA, Feldman EL, Gibson SB, Taroni F, Ratti A, Gellera C, Van Damme P, Robberecht W, Fratta P, Sabatelli M, Lunetta C, Ludolph AC, Andersen PM, Weishaupt JH, Camu W, Trojanowski JQ, Van Deerlin VM, Brown RH, Jr., van den Berg LH, Veldink JH, Harms MB, Glass JD, Stone DJ, Tienari P, Silani V, Chio A, Shaw CE, Traynor BJ, Landers JE. Genome-wide Analyses Identify KIF5A as a Novel ALS Gene. **Neuron**. 2018;97(6):1268-1283 e1266. doi: 10.1016/j.neuron.2018.02.027. PubMed PMID: 29566793; PMCID: PMC5867896.
158. Petersen CP, Meyer AR, De Salvo C, Choi E, Schlegel C, Petersen A, Engevik AC, Prasad N, Levy SE, Peebles RS, Pizarro TT, Goldenring JR. A signalling cascade of IL-33 to IL-13 regulates metaplasia in the mouse stomach. **Gut**. 2018;67(5):805-817. doi: 10.1136/gutjnl-2016-312779. PubMed PMID: 28196875; PMCID: PMC5681443.
159. Liu N, Schoch K, Luo X, Pena LDM, Bhavana VH, Kukolich MK, Stringer S, Powis Z, Radtke K, Mroske C, Deak KL, McDonald MT, McConkie-Rosell A, Markert ML, Kranz PG, Stong N, Need AC, Bick D, Amaral MD, Worthey EA, Levy S, Undiagnosed Diseases N, Wangler MF, Bellen HJ, Shashi V, Yamamoto S. Functional variants in TBX2 are associated with a syndromic cardiovascular and skeletal developmental disorder. **Hum Mol Genet**. 2018. doi: 10.1093/hmg/ddy146. PubMed PMID: 29726930.
160. Selvan N, George S, Serajee FJ, Shaw M, Hobson L, Kalscheuer VM, Prasad N, Levy SE, Taylor J, Afitmos S, Schwartz CE, Huq AM, Gecz J, Wells L. O-GlcNAc transferase missense mutations linked to X-linked intellectual disability deregulate genes involved in cell fate determination and signaling. **J Biol Chem**. 2018. doi: 10.1074/jbc.RA118.002583. PubMed PMID: 29769320.

161. Wang Z, Wilson CL, Easton J, Thrasher A, Mulder H, Liu Q, Hedges DJ, Wang S, Rusch MC, Edmonson MN, Levy S, Lanctot JQ, Caron E, Shelton K, Currie K, Lear M, Patel A, Rosencrance C, Shao Y, Vadodaria B, Yergeau D, Sapkota Y, Brooke RJ, Moon W, Rampersaud E, Ma X, Chang TC, Rice SV, Pepper C, Zhou X, Chen X, Chen W, Jones A, Boone B, Ehrhardt MJ, Krasin MJ, Howell RM, Phillips NS, Lewis C, Srivastava D, Pui CH, Kesserwan CA, Wu G, Nichols KE, Downing JR, Hudson MM, Yasui Y, Robison LL, Zhang J. Genetic Risk for Subsequent Neoplasms Among Long-Term Survivors of Childhood Cancer. **J Clin Oncol**. 2018;JCO2018778589. doi: 10.1200/JCO.2018.77.8589. PubMed PMID: 29847298.
162. Carlson J, Locke AE, Flickinger M, Zawistowski M, Levy S, Myers RM, Boehnke M, Kang HM, Scott LJ, Li JZ, Zollner S, Bipolar Sequencing Consortium. Extremely rare variants reveal patterns of germline mutation rate heterogeneity in humans. **Nat Commun**. 2018;9(1):3753. doi: 10.1038/s41467-018-05936-5. PubMed PMID: 30218074; PMCID: PMC6138700.

Exhibit B

MATERIALS AND DATA CONSIDERED

Literature

Acencio, Milena M. P., Evaldo Marchi, Lisete R. Teixeira, Bruna Rocha Silva, Juliana Sanchez Silva, Carlos Sergio Rocha Silva, Vanessa Adelia Alvarenga, Leila Antonangelo, Francisco Suso Vargas, and Vera Luiza Capelozzi. “Talc Particles and Pleural Mesothelium Interface Modulate Apoptosis and Inflammation.” *Pathology* 46, no. S2 (2014): S76.

Acheson, E D, M J Gardner, E C Pippard, and L P Grime. “Mortality of Two Groups of Women Who Manufactured Gas Masks from Chrysotile and Crocidolite Asbestos: A 40-Year Follow-Up.” *British Journal of Industrial Medicine* 39, no. 4 (November 1982): 344–48.

Adami, H.O., Hsieh, C.C., Lambe, M., Trichopoulos, D., Leon, D., Persson, I., Ekblom, A., and Janson, P.O. (1994). Parity, age at first childbirth, and risk of ovarian cancer. *Lancet* 344, 1250-1254.

Agic, A., Xu, H., Finas, D., Banz, C., Diedrich, K., and Hornung, D. (2006). Is endometriosis associated with systemic subclinical inflammation? *Gynecol Obstet Invest* 62, 139-147.

Akhtar, Mohd Javed, Maqsood Ahamed, M.A. Majeed Khan, Salman A. Alrokayan, Iqbal Ahmad, and Sudhir Kumar. “Cytotoxicity and Apoptosis Induction by Nanoscale Talc Particles from Two Different Geographical Regions in Human Lung Epithelial Cells.” *Environmental Toxicology* 29 (2014): 394–406. <https://doi.org/10.1002/tox.21766>.

Akhtar, Mohd Javed, Sudhir Kumar, Ramesh Chandra Murthy, Mohd Ashquin, Mohd Imran Khan, Govil Patil, and Iqbal Ahmad. “The Primary Role of Iron-Mediated Lipid Peroxidation in the Differential Cytotoxicity Caused by Two Varieties of Talc Nanoparticles on A549 Cells and Lipid Peroxidation Inhibitory Effect Exerted by Ascorbic Acid.” *Toxicology in Vitro: An International Journal Published in Association with BIBRA* 24, no. 4 (June 2010): 1139–47. <https://doi.org/10.1016/j.tiv.2010.03.002>.

Albu, Cristina-Crenguta. “The Genetics of Ovarian Cancer.” *SMGroup*, (November 3, 2017).

Arellano-Orden, Elena, Auxiliadora Romero-Falcon, Jose Martin Juan, Manuel Ocana Jurado, Francisco Rodriguez-Panadero, and Ana Montes-Worboys. “Small Particle-Size Talc Is Associated with Poor Outcome and Increased Inflammation in Thoracoscopic Pleurodesis.” *Respiration* 86 (2013): 201–9. <https://doi.org/10.1159/000342042>.

“ATSDR - Toxicological Profile: Asbestos.” Accessed August 16, 2018. <https://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=30&tid=4>.

Aust, A.E., Cook, P.M., and Dodson, R.F. Morphological and chemical mechanisms of elongated mineral particle toxicities. *J Toxicol and Environ Health, Part B.* (2011) 14:40-75.

Balkwill, F., and Mantovani, A. (2001). Inflammation and cancer: back to Virchow? *Lancet* 357, 539-545.

Banerjee, S., and Kaye, S.B. (2013). New strategies in the treatment of ovarian cancer: current clinical perspectives and future potential. *Clin Cancer Res* 19, 961-968.

Barnes, D.R., and Antoniou, A.C. (2012). Unravelling modifiers of breast and ovarian cancer risk for BRCA1 and BRCA2 mutation carriers: update on genetic modifiers. *J Intern Med* 271, 331-343.

Begg, Melissa D., and Dana March. "Cause and Association: Missing the Forest for the Trees." *American Journal of Public Health* 108, No. 5 (May 2018): 620–620.

Belotte, J., Fletcher, N.M., Saed, M.G., Abusamaan, M.S., Dyson, G, Diamond, M.P., Saed, G.M. (2015) A single nucleotide polymorphism in catalase is strongly associated with ovarian cancer survival. *PLoS ONE* 10(8): e0135739. Doi: 10.1371/journal.pone.0135739.

Belotte, Jimmy, Nicole M. Fletcher, Awoniyi O. Awonuga, Mitchell Alexis, Husam M. Abu-Soud, Ghassan M. Saed, Michael P. Diamond, and Mohammed G. Saed. "The Role of Oxidative Stress in the Development of Cisplatin Resistance in Epithelial Ovarian Cancer." *Reproductive Sciences* 21, no. 4 (2014): 503–8.

Berek, J.S., Crum, C., and Friedlander, M. (2012). Cancer of the ovary, fallopian tube, and peritoneum. *Int J Gynaecol Obstet* 119 Suppl 2, S118-129.

Berge, Wera, Kenneth Mundt, Hung Luu, and Paolo Boffetta. "Genital Use of Talc and Risk of Ovarian Cancer: A Meta-Analysis." *European Journal of Cancer Prevention*, July 2017.

Berry, G., M. L. Newhouse, and J. C. Wagner. "Mortality from All Cancers of Asbestos Factory Workers in East London 1933-80." *Occupational and Environmental Medicine* 57, no. 11 (November 2000): 782–85.

Bertolotti, Marinella, Daniela Ferrante, Dario Mirabelli, Mario Botta, Marinella Nonnato, Annalisa Todesco, Benedetto Terracini, and Corrado Magnani. "[Mortality in the cohort of the asbestos cement workers in the Eternit plant in Casale Monferrato (Italy)]." *Epidemiologia E Prevenzione* 32, no. 4–5 (October 2008): 218–28.

Blount, A.M. (1991). Amphibole content of cosmetic and pharmaceutical talcs. *Environ Health Perspect* 94, 225-230.

Blumenkrantz, M. J., N. Gallagher, R. A. Bashore, and H. Tenckhoff. "Retrograde Menstruation in Women Undergoing Chronic Peritoneal Dialysis." *Obstetrics and Gynecology* 57, no. 5 (May 1981): 667–70.

Bodmer, M., Becker, C., Meier, C., Jick, S.S., and Meier, C.R. (2011). Use of metformin and the risk of ovarian cancer: a case-control analysis. *Gynecol Oncol* 123, 200-204.

Bonovas, S., Filioussi, K., and Sitaras, N.M. (2005). Do nonsteroidal anti-inflammatory drugs affect the risk of developing ovarian cancer? A meta-analysis. *Br J Clin Pharmacol* 60, 194-203.

Booth, M, V Beral, and P Smith. "Risk Factors for Ovarian Cancer: A Case-Control Study." *British Journal of Cancer* 60, No. 4 (October 1989): 592-98.

Boorman, G. A., and J. C. Seely. "The Lack of an Ovarian Effect of Lifetime Talc Exposure in F344/N Rats and B6C3F1 Mice." *Regulatory Toxicology and Pharmacology: RTP* 21, no. 2 (April 1995): 242-43.

Bowtell, D.D. (2010). The genesis and evolution of high-grade serous ovarian cancer. *Nat Rev Cancer* 10, 803-808.

Buz'Zard, Amber R., and Benjamin H. S. Lau. "Pycnogenol® Reduces Talc-Induced Neoplastic Transformation in Human Ovarian Cell Cultures." *Phytotherapy Research* 21, No. 6 (June 2007): 579-86.

Camargo, M.C., Stayner, L.T., Straif, K., Reina, M., Al-Alem, U., Demers, P.A., and Landrigan, P.J. (2011). Occupational exposure to asbestos and ovarian cancer: a meta-analysis. *Environ Health Perspect* 119, 1211-1217.

Carr, C.J. "Talc: Consumer Uses and Health Perspectives" 21 (1995): 211-15.

Casagrande, J.T., Louie, E.W., Pike, M.C., Roy, S., Ross, R.K., and Henderson, B.E. (1979). "Incessant ovulation" and ovarian cancer. *Lancet* 2, 170-173.

Chan, J.K., Cheung, M.K., Husain, A., Teng, N.N., West, D., Whittemore, A.S., Berek, J.S., and Osann, K. (2006). Patterns and progress in ovarian cancer over 14 years. *Obstet Gynecol* 108, 521-528.

Chang, Stella, and Harvey A. Risch. "Perineal Talc Exposure and Risk of Ovarian Carcinoma." *Cancer* 79, No. 12 (June 15, 1997): 2396-2401.

Charbonneau, B., Goode, E.L., Kalli, K.R., Knutson, K.L., and Derycke, M.S. (2013). The immune system in the pathogenesis of ovarian cancer. *Crit Rev Immunol* 33, 137-164.

Chen Yong. "Risk Factors for Epithelial Ovarian Cancer in Beijing, China." *International Journal of Epidemiology*, 21, No. 1 (1992): 23-29.

Chen, L-M, et al. "Epithelial Carcinoma of the Ovary, Fallopian Tube, and Peritoneum: Epidemiology and Risk Factors - UpToDate," 2018.
<https://www.uptodate.com/contents/epithelial-carcinoma-of-the-ovary-fallopian-tube-and-peritoneum-epidemiology-and-risk-factors?search=Epithelial%20carcinoma%20of%20the%20ovary,%20fallopian%20tube,%20and%20peritoneum:%20Epidemiology%20and%20risk%20factors&so>

urce=search_result&selectedTitle=1~150&usage_type=default&display_rank=1.

Committee on Practice Bulletins–Gynecology, Committee on Genetics, Society of Gynecologic Oncology. “Practice Bulletin No 182: Hereditary Breast and Ovarian Cancer Syndrome.” *Obstetrics and Gynecology* 130, no. 3 (2017): e110–26.

Cook, L. S., M. L. Kamb, and N. S. Weiss. “Perineal Powder Exposure and the Risk of Ovarian Cancer.” *American Journal of Epidemiology* 145, No. 5 (March 1, 1997): 459–65.

Coussens, L.M., Tinkle, C.L., Hanahan, D., and Werb, Z. (2000). MMP-9 supplied by bone marrow-derived cells contributes to skin carcinogenesis. *Cell* 103, 481-490.

Coussens, L.M., and Werb, Z. (2002). Inflammation and cancer. *Nature* 420, 860-867.

Cralley, L. J., M. M. Key, D. H. Groth, W. S. Lainhart, and R. M. Ligo. “Fibrous and Mineral Content of Cosmetic Talcum Products.” *American Industrial Hygiene Association Journal* 29, no. 4 (August 1968): 350–54.

Cramer, Daniel. “Perineal Talc Exposure and Subsequent Epithelial Ovarian Cancer: A Case-Control Study.” *Obstetrics & Gynecology*, (1999).

Cramer, Daniel, et al. “Genital Talc Exposure and Risk of Ovarian Cancer.” *Int. J. Cancer*: 81 (1999): 351-356.

Cramer, D. W., W. R. Welch, R. E. Scully, and C. A. Wojciechowski. “Ovarian Cancer and Talc: A Case-Control Study.” *Cancer* 50, no. 2 (July 15, 1982): 372–76.

Cramer, Daniel W., Linda Titus-Ernstoff, John R. McKolanis, William R. Welch, Allison F. Vitonis, Ross S. Berkowitz, and Olivera J. Finn. “Conditions Associated with Antibodies Against the Tumor-Associated Antigen MUC1 and Their Relationship to Risk for Ovarian Cancer.” *Cancer Epidemiology Biomarkers & Prevention* 14, no. 5 (May 1, 2005): 1125–31.

Cramer, Daniel W., Allison F. Vitonis, Kathryn L. Terry, William R. Welch, and Linda J. Titus. “The Association Between Talc Use and Ovarian Cancer: A Retrospective Case–Control Study in Two US States.” *Epidemiology* 27, No. 3 (May 2016): 334–46.

Cramer, Daniel W., William R. Welch, Robert E. Scully, and Carol A. Wojciechowski. “Ovarian Cancer and Talc. A Case-Control Study.” *Cancer* 50, No. 2 (July 15, 1982): 372–76.

Crusz, Shanthini M., and Frances R Balkwill. “Inflammation and Cancer: Advances and New Agents.” *Nature Reviews Clinical Oncology* 12 (October 2015): 584–96.

Dixon, Suzanne C., Christina M. Nagle, Nicolas Wentzensen, Britton Trabert, Alicia Beeghly-Fadiel, Joellen M. Schildkraut, Kirsten B. Moysich, et al. “Use of Common Analgesic Medications and Ovarian Cancer Survival: Results from a Pooled Analysis in the Ovarian Cancer Association Consortium.” *British Journal of Cancer* 116, no. 9 (April 25, 2017):

1223–28.

Dvorak, H.F. (1986). Tumors: wounds that do not heal. Similarities between tumor stroma generation and wound healing. *N Engl J Med* 315, 1650-1659.

Egli, G. E., and M. Newton. “The Transport of Carbon Particles in the Human Female Reproductive Tract.” *Fertility and Sterility* 12 (April 1961): 151–55.

Eng, Kevin H., J. Brian Szender, John Lewis Etter, Jasmine Kaur, Samantha Poblete, Ruea-Yea Huang, Qianqian Zhu, et al. “Paternal Lineage Early Onset Hereditary Ovarian Cancers: A Familial Ovarian Cancer Registry Study.” *PLoS Genetics* 14, no. 2 (February 2018): e1007194.

Fasching, Peter A., Simon Gayther, Leigh Pearce, Joellen M. Schildkraut, Ellen Goode, Falk Thiel, Georgia Chenevix-Trench, et al. “Role of Genetic Polymorphisms and Ovarian Cancer Susceptibility.” *Molecular Oncology* 3, No. 2 (April 2009): 171–81.

FDA. “Ltr to Samuel S. Epstein, M.D., RE: Docket Numbers 94P-0420 and FDA-2008-P-0309-0001 /CP,” April 1, 2017.

Fernandes, José Veríssimo, Ricardo Ney Oliveira Cobucci, Carlos André Nunes Jatobá, Thales Allyrio Araújo de Medeiros Fernandes, Judson Welber Veríssimo de Azevedo, and Josélio Maria Galvão de Araújo. “The Role of the Mediators of Inflammation in Cancer Development.” *Pathology & Oncology Research* 21, no. 3 (July 2015): 527–34.

Ferrante, Daniela, Marinella Bertolotti, Annalisa Todesco, Dario Mirabelli, Benedetto Terracini, and Corrado Magnani. “Cancer Mortality and Incidence of Mesothelioma in a Cohort of Wives of Asbestos Workers in Casale Monferrato, Italy.” *Environmental Health Perspectives* 115, no. 10 (October 2007): 1401–5.

Fiume, Monice M., Ivan Boyer, Wilma F. Bergfeld, Donald V. Belsito, Ronald A. Hill, Curtis D. Klaassen, Daniel C. Liebler, et al. “Safety Assessment of Talc as Used in Cosmetics.” *International Journal of Toxicology* 34, no. 1 suppl (July 1, 2015): 66S-129S.

Fletcher, N.M., Belotte, J., Saed, M.G., Memaj, I., Diamond, M.P., Morris, R.T., Saed, G.M. Specific point mutations in key redox enzymes are associated with chemoresistance in epithelial ovarian cancer. *Free Radical Biology and Medicine* (2017) 102:122-132.

Fletcher, Nicole., Ira Memaj, Ghassan M. Saed. “Talcum Powder Enhances Oxidative Stress in Ovarian Cancer Cells.” *Reproductive Sciences*, 25 Supp. 1 (March 2018): 214A-15A.

Fletcher, N.M., Saed, G.M. (2018). Talcum Powder enhances cancer antigen 125 levels in ovarian cancer cells and in normal ovarian epithelial cells. LB-044. Poster presented at: Society for Reproductive Investigation. 65th annual meeting. San Diego, CA.

Folkins, Ann K. “Chapter 24 - Assessing Pelvic Epithelial Cancer Risk and Intercepting Early Malignancy,” *Diagnostic Gynecologic and Obstetric Pathology (Third Edition)*, (2018):

844-864.

Franklin, R.A., and Li, M.O. (2016). Ontogeny of Tumor-associated Macrophages and Its Implication in Cancer Regulation. *Trends Cancer* 2, 20-34.

Freedman, Ralph S, Michael Deavers, Jinsong Liu, and Ena Wang. "Peritoneal Inflammation – A Microenvironment for Epithelial Ovarian Cancer (EOC)." *Journal of Translational Medicine* 2, no. 23 (2004).

Friebel, Tara M., Susan M. Domchek, and Timothy R. Rebbeck. "Modifiers of Cancer Risk in BRCA1 and BRCA2 Mutation Carriers: Systematic Review and Meta-Analysis." *Journal of the National Cancer Institute* 106, no. 6 (June 2014): dju091.

Galea, Sandro and Roger D. Vaughan. "Moving Beyond the Cause Constraint: A Public Health of Consequence." *AJPH*, 108, No. 5 (May 2018): 602-603.

Gates, M. A., B. A. Rosner, J. L. Hecht, and S. S. Tworoger. "Risk Factors for Epithelial Ovarian Cancer by Histologic Subtype." *American Journal of Epidemiology* 171, No. 1 (2010): 45–53.

Gates, M. A., S. S. Tworoger, K. L. Terry, L. Titus-Ernstoff, B. Rosner, I. De Vivo, D. W. Cramer, and S. E. Hankinson. "Talc Use, Variants of the GSTM1, GSTT1, and NAT2 Genes, and Risk of Epithelial Ovarian Cancer." *Cancer Epidemiol Biomarkers Prev.* 17, No. 9 (September 2008): 2436–44.

Germani, D., S. Belli, C. Bruno, M. Grignoli, M. Nesti, R. Pirastu, and P. Comba. "Cohort Mortality Study of Women Compensated for Asbestosis in Italy." *American Journal of Industrial Medicine* 36, no. 1 (July 1999): 129–34.

Gertig, Dorota M., David J. Hunter, Daniel W. Cramer, Graham A. Colditz, Frank E. Speizer, Walter C. Willett, and Susan E. Hankinson. "Prospective Study of Talc Use and Ovarian Cancer." *J Natl Cancer Inst* 92, No. 3 (February 2, 2000): 249–52.

Ghio, Andrew J., Joleen M. Soukup, Lisa A. Dailey, Judy H. Richards, Jennifer L. Turi, Elizabeth N. Pavlisko, and Victor L. Roggli. "Disruption of Iron Homeostasis in Mesothelial Cells after Talc Pleurodesis." *American Journal of Respiratory Cell and Molecular Biology* 46, no. 1 (January 1, 2012): 80–86.

Godard, Beatrice, William D. Foulkes, Diane Provencher, Jean-Sebastien Brunet, Patricia N. Tonin, Anne-Marie Mes-Masson, Steven A. Narod, and Parviz Ghadirian. "Risk Factors for Familial and Sporadic Ovarian Cancer among French Canadians: A Case-Control Study." *Am J Obstet Gynecol* 179, No. 2 (August 1998): 403–10.

Gonzalez, Nicole L., Katie M. O'Brien, Aimee A. D'Aloisio, Dale P. Sandler, and Clarice R. Weinberg. "Douching, Talc Use, and Risk of Ovarian Cancer." *Epidemiology* 27, No. 6 (November 2016): 797–802.

Gordon, Ronald E., Sean Fitzgerald, and James Millette. "Asbestos in Commercial Cosmetic

Talcum Powder as a Cause of Mesothelioma in Women.” *International Journal of Occupational and Environmental Health* 20, no. 4 (October 2014): 318–32.

Green, Adèle, David Purdie, Christopher Bain, Victor Siskind, Peter Russell, Michael Quinn, and Bruce Ward. “Tubal Sterilisation, Hysterectomy and Decreased Risk of Ovarian Cancer.” *Int. J Cancer* 71, No. 6 (June 11, 1997): 948–51.

Grivennikov, Sergei I., Florian R. Greten, and Michael Karin. “Immunity, Inflammation, and Cancer.” *Cell* 140, no. 6 (March 19, 2010): 883–99.

Gross, Alan J. and Paul H. Berg. “A Meta-Analytical Approach Examining the Potential Relationship Between Talc Exposure and Ovarian Cancer.” *Journal of Exposure Analysis and Environmental Epidemiology*, 5, No. 2 (1995): 181-195.

Halme, J., M. G. Hammond, J. F. Hulka, S. G. Raj, and L. M. Talbert. “Retrograde Menstruation in Healthy Women and in Patients with Endometriosis.” *Obstetrics and Gynecology* 64, no. 2 (August 1984): 151–54.

Hamilton, T.C., Fox, H., Buckley, C.H., Henderson, W.J., and Griffiths, K. Effects of talc on the rat ovary. *Br. J. Exp. Path.* (1984) 65: 101-106.

Harlow, Bernard L., and Noel S. Weiss. “A Case-Control Study of Borderline Ovarian Tumors: The Influence of Perineal Exposure to Talc.” *American Journal of Epidemiology* 130, No. 2 (August 1989): 390–94.

Harlow, Bernard L., Daniel W. Cramer, Debra A. Bell and William R. Welch. “Perineal Exposure to Talc and Ovarian Cancer Risk.” *Obstet Gynecol* 80, No. 1 (1992): 19-26.

Harper, A.K., Saed, G.M. Talc induces a pro-oxidant state in normal and ovarian cancer cells through gene point mutations in key redox enzymes. Accepted for presentation at SGO meeting 2019. [In Press].

Hartge, Patricia, Robert Hoover, Linda Leshner and Larry McGowan. “Talc and Ovarian Cancer.” *JAMA*, 250, No. 14 (1983): 1844.

Hein, M.J., Stayner, L.T., Lehman, E., Dement, J.M. Follow-up study of chrysotile textile workers: cohort mortality and exposure-response. *Occup Environ Med* (2007) 64:616-625.

Heller, D.S., Gordon, R.E., Westhoff, C., and Gerber, S. (1996). Asbestos exposure and ovarian fiber burden. *Am J Ind Med* 29, 435-439.

Henderson, W. J., T. C. Hamilton, M. S. Baylis, C. G. Pierrepoint, and K. Griffiths. “The Demonstration of the Migration of Talc from the Vagina and Posterior Uterus to the Ovary in the Rat.” *Environmental Research* 40, no. 2 (August 1986): 247–50.

Henderson, W. J., C. A. Joslin, A. C. Turnbull, and K. Griffiths. “Talc and Carcinoma of the Ovary and Cervix.” *The Journal of Obstetrics and Gynaecology of the British Commonwealth*

78, no. 3 (March 1971): 266–72.

Hernán, Miguel A. “The C-Word: Scientific Euphemisms Do Not Improve Causal Inference From Observational Data.” *American Journal of Public Health* 108, No. 5 (May 2018): 616–19.

Hesterberg, T.W., Butterick, C.J., Oshimura, M., Brody, A.R., and Barrett, J.C. (1986). Role of phagocytosis in Syrian hamster cell transformation and cytogenetic effects induced by asbestos and short and long glass fibers. *Cancer Res* 46, 5795-5802.

Hill, Austin Bradford. “The Environment and Disease: Association or Causation?” *Proceedings of the Royal Society of Medicine* 58, no. 5 (May 1965): 295–300.

Hillegass, Jedd M., Arti Shukla, Maximilian B. MacPherson, Jeffrey P. Bond, Chad Steele, and Brooke T. Mossman. “Utilization of Gene Profiling and Proteomics to Determine Mineral Pathogenicity in a Human Mesothelial Cell Line (LP9/TERT-1).” *Journal of Toxicology and Environmental Health. Part A* 73, no. 5 (January 2010): 423–36.

Houghton, S. C., K. W. Reeves, S. E. Hankinson, L. Crawford, D. Lane, J. Wactawski-Wende, C. A. Thomson, J. K. Ockene, and S. R. Sturgeon. “Perineal Powder Use and Risk of Ovarian Cancer.” *Journal of the National Cancer Institute* 106, No. 9 (September 10, 2014).

Huncharek, Michael, J.F. Geschwind and Bruce Kupelnick. “Perineal Application of Cosmetic Talc and Risk of Invasive Epithelial Ovarian Cancer: A Meta-analysis of 11,933 Subjects from Sixteen Observational Studies.” *Anticancer Research*, 25 (2003): 1955-1960.

Huncharek, Michael, Joshua Muscat, Adedayo Onitilo, and Bruce Kupelnick. “Use of Cosmetic Talc on Contraceptive Diaphragms and Risk of Ovarian Cancer: A Meta-Analysis of Nine Observational Studies.” *European Journal of Cancer Prevention* 16, No. 5 (October 2007): 422–29.

Hunn, Jessica, and Gustavo C. Rodriguez. “Ovarian Cancer: Etiology, Risk Factors, and Epidemiology.” *Clinical Obstetrics and Gynecology* 55, No. 1 (March 2012): 3–23.

“Inflammation: A Hidden Path to Breaking the Spell of Ovarian Cancer.” *Cell Cycle* 8, no. 19 (2009): 3107–11.

Institute of Medicine (US) Committee on Asbestos: Selected Health Effects. *Asbestos: Selected Cancers*. The National Academies Collection: Reports Funded by National Institutes of Health. Washington (DC): National Academies Press (US), 2006.

International Agency for Research on Cancer (IARC). “IARC Monographs on the Evaluation of Carcinogenic Risks to Humans – IARC : Asbestos,” 1977.

International Agency for Research on Cancer (IARC), “Cobalt in Hard Metals and Cobalt Sulfate, Gallium Arsenide, Indium Phosphide and Vanadium Pentoxide,” IARC Monograph No. 86 (2006).

International Agency for Research on Cancer (IARC), “Arsenic, Metals, Fibres, and Dusts,” IARC Monograph No. 100C (2009).

International Agency for Research on Cancer (IARC), “Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42,” IARC Supplement No. 7 (1987).

International Agency for Research on Cancer (IARC), “Silica and Some Silicates,” IARC Monograph No. 42 (1987).

International Agency for Research on Cancer (IARC), “Carbon Black, Titanium Dioxide, and Talc,” IARC Monograph No. 93 (2010).

International Agency for Research on Cancer (IARC), “Arsenic, Metals, Fibres, and Dusts,” IARC Monograph No. 100C (2012).

International Agency for Research on Cancer (IARC), “Mechanisms of Fibre Carcinogenesis,” IARC Scientific Publications, No. 140 (1996).

Irie, H., Banno, K., Yanokura, M., Iida, M., Adachi, M., Nakamura, K., Umene, K., Nogami, Y., Masuda, K., Kobayashi, Y., *et al.* (2016). Metformin: A candidate for the treatment of gynecological tumors based on drug repositioning. *Oncol Lett* 11, 1287-1293.

Iturralde, M., and P. F. Venter. “Hysterosalpingo-Radionuclide Scintigraphy (HERS).” *Seminars in Nuclear Medicine* 11, no. 4 (October 1981): 301–14.

Jaurand, M.C. Mechanisms of fiber-induced genotoxicity. *Environ Health Perspect* (1997) 105(Suppl 5):1073-1084.

Jayson, G.C., Kohn, E.C., Kitchener, H.C., and Ledermann, J.A. (2014). Ovarian cancer. *Lancet* 384, 1376-1388.

Jervis, Sarah, Honglin Song, Andrew Lee, Ed Dicks, Jonathan Tyrer, Patricia Harrington, Douglas F. Easton, Ian J. Jacobs, Paul P. D. Pharoah, and Antonis C. Antoniou. “Ovarian Cancer Familial Relative Risks by Tumour Subtypes and by Known Ovarian Cancer Genetic Susceptibility Variants.” *Journal of Medical Genetics* 51, no. 2 (February 2014): 108–13.

Jia, D., Nagaoka, Y., Katsumata, M., and Orsulic, S. (2018). Inflammation is a key contributor to ovarian cancer cell seeding. *Sci Rep* 8, 12394.

Jones, Richard E., and Kristin H. Lopez. “Human Reproductive Biology - 4th Edition Chapter 9 - Gamete Transport and Fertilization.” In *Human Reproductive Biology*, Third., 159–73. San Diego: Academic Press, 2006.

Jordan, S.J., Cushing-Haugen, K.L., Wicklund, K.G., Doherty, J.A., and Rossing, M.A. (2012). Breast-feeding and risk of epithelial ovarian cancer. *Cancer Causes Control* 23, 919-927.

Kane, AB, P Boffetta, R Saracci, and JD Wilbourn. "Mechanisms of Fibre Carcinogenesis." IARC, 1996.

Karageorgi, S., M. A. Gates, S. E. Hankinson, and I. De Vivo. "Perineal Use of Talcum Powder and Endometrial Cancer Risk." *Cancer Epidemiology Biomarkers & Prevention* 19, No. 5 (May 1, 2010): 1269–75.

Kauff, Noah D., Nandita Mitra, Mark E. Robson, Karen E. Hurley, Shaokun Chuai, Deborah Goldfrank, Eve Wadsworth, et al. "Risk of Ovarian Cancer in BRCA1 and BRCA2 Mutation-Negative Hereditary Breast Cancer Families." *Journal of the National Cancer Institute* 97, no. 18 (September 21, 2005): 1382–84.

Keskin, N., Teksen, Y.A., Ongun, E.G., Ozay, Y., Saygili, H. Does long-term talc exposure have a carcinogenic effect on the female genital system of rats? An experimental pilot study. *Arch Gynecol Obstet.* (2009). 280:925-931.

Kisielewski, R., Tolwinska, A., Mazurek, A., and Laudanski, P. (2013). Inflammation and ovarian cancer--current views. *Ginekol Pol* 84, 293-297.

Kissler, Stefan, Ernst Siebzehnuebl, Joachim Kohl, Anja Mueller, Nadja Hamscho, Regine Gaetje, Andre Ahr, Achim Rody, and Manfred Kaufmann. "Uterine Contractility and Directed Sperm Transport Assessed by Hysterosalpingoscintigraphy (HSSG) and Intrauterine Pressure (IUP) Measurement." *Acta Obstetricia Et Gynecologica Scandinavica* 83, no. 4 (April 2004): 369–74.

Khan, Mohd Imran, AmoghA. Sahasrabuddhe, Govil Patil, Mohd Javed Akhtar, Mohd Ashquin, and Iqbal Ahmad. "Nano-Talc Stabilizes TNF- α m-RNA in Human Macrophages." *Journal of Biomedical Nanotechnology* 7, no. 1 (January 1, 2011): 112–13.

Kiraly, Orsolya, Guanyu Gong, Werner Olipitz, Sureshkumar Muthupalani, and Bevin P. Engelward. "Inflammation-Induced Cell Proliferation Potentiates DNA Damage-Induced Mutations In Vivo." *PLoS Genetics*, February 3, 2015.

Kunz, G., D. Beil, H. Deiniger, A. Einspanier, G. Mall, and G. Leyendecker. "The Uterine Peristaltic Pump. Normal and Impeded Sperm Transport within the Female Genital Tract." *Advances in Experimental Medicine and Biology* 424 (1997): 267–77.

Kurta, M. L., K. B. Moysich, J. L. Weissfeld, A. O. Youk, C. H. Bunker, R. P. Edwards, F. Modugno, R. B. Ness, and B. Diergaarde. "Use of Fertility Drugs and Risk of Ovarian Cancer: Results from a U.S.-Based Case-Control Study." *Cancer Epidemiol Biomarkers Prev.* 21, No. 8 (August 1, 2012): 1282–92.

Landen, Charles N., Michael J. Birrer, and Anil K. Sood. "Early Events in the Pathogenesis of Epithelial Ovarian Cancer." *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology* 26, no. 6 (February 20, 2008): 995–1005.

Langseth, H., Johansen, B.V., Nesland, J.M., and Kjaerheim, K. (2007). Asbestos fibers in ovarian tissue from Norwegian pulp and paper workers. *Int J Gynecol Cancer* 17, 44-49.

Langseth, H, S E Hankinson, J Siemiatycki, and E Weiderpass. "Perineal Use of Talc and Risk of Ovarian Cancer." *J Epidemiol Community Health* 62, No. 4 (April 1, 2008): 358–60.

Langseth, Hilde, and Kristina Kjærheim. "Ovarian Cancer and Occupational Exposure among Pulp and Paper Employees in Norway." *Scand J Work, Environ Health* 30, No. 5 (October 2004): 356–61.

Lee, Jennifer S., Esther M. John, Valerie McGuire, Anna Felberg, Kimberly L. Ostrow, Richard A. DiCioccio, Frederick P. Li, Alexander Miron, Dee W. West, and Alice S. Whittemore. "Breast and Ovarian Cancer in Relatives of Cancer Patients, with and without BRCA Mutations." *Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology* 15, no. 2 (February 2006): 359–63.

Levanon, K., Crum, C., Drapkin, R. New insights into the pathogenesis of serous ovarian cancer and its clinical impact. *J Clin Oncol.* (2008). Nov 10;26(32):5284-93.

Li, D. (2011). Metformin as an antitumor agent in cancer prevention and treatment. *J Diabetes* 3, 320-327.

Lin, H.W., Tu, Y.Y., Lin, S.Y., Su, W.J., Lin, W.L., Lin, W.Z., Wu, S.C., and Lai, Y.L. (2011). Risk of ovarian cancer in women with pelvic inflammatory disease: a population-based study. *Lancet Oncol* 12, 900-904.

Liou, Geou-Yarh, and Peter Storz. "Reactive Oxygen Species in Cancer." *Free Radical Research* 44, no. 5 (May 2010): 476–96.

Liu, Y., and Cao, X. (2015). The origin and function of tumor-associated macrophages. *Cell Mol Immunol* 12, 1-4.

Lockey, J. E. "Nonasbestos Fibrous Minerals." *Clinics in Chest Medicine* 2, no. 2 (May 1981): 203–18.

"Longo - Feb 2018 MAS Report," 2018.

Longo, William E., and Mark W. Rigler. "The Analysis of Johnson & Johnson's Historical Baby Powder & Shower to Shower Products from the 1960's to the Early 1990's for Amphibole Asbestos," November 14, 2018.

Longo, William E., Mark W. Rigler, and William B. Egeland. "Below the Waist Application of Johnson & Johnson Baby Powder." Materials Analytical Service, LLC, September 2017.

Maccio, A., and Madeddu, C. (2012). Inflammation and ovarian cancer. *Cytokine* 58, 133-147.

Mabuchi, S., Kawase, C., Altomare, D.A., Morishige, K., Sawada, K., Hayashi, M., Tsujimoto, M., Yamoto, M., Klein-Szanto, A.J., Schilder, R.J., *et al.* (2009). mTOR is a promising therapeutic target both in cisplatin-sensitive and cisplatin-resistant clear cell carcinoma of the ovary. *Clin Cancer Res* 15, 5404-5413.

Magnani, C., D. Ferrante, F. Barone-Adesi, M. Bertolotti, A. Todesco, D. Mirabelli, and B. Terracini. "Cancer Risk after Cessation of Asbestos Exposure: A Cohort Study of Italian Asbestos Cement Workers." *Occupational and Environmental Medicine* 65, no. 3 (March 2008): 164–70.

Mahdavi, A., Pejovic, T., and Nezhat, F. (2006). Induction of ovulation and ovarian cancer: a critical review of the literature. *Fertil Steril* 85, 819-826.

Mäki-Nevala, Satu, Virinder Kaur Sarhadi, Aija Knuuttila, Ilari Scheinin, Pekka Ellonen, Sonja Lagström, Mikko Rönty, *et al.* "Driver Gene and Novel Mutations in Asbestos-Exposed Lung Adenocarcinoma and Malignant Mesothelioma Detected by Exome Sequencing." *Lung* 194, no. 1 (February 2016): 125–35.

Mallen, Adrienne R., Mary K. Townsend, and Shelley S. Tworoger. "Risk Factors for Ovarian Carcinoma." *Hematol Oncol Clin N Am*, September 2018. <https://doi.org/10.1016/j.hoc.2018.07.002>.

Mantovani, A., Bottazzi, B., Colotta, F., Sozzani, S., and Ruco, L. (1992a). The origin and function of tumor-associated macrophages. *Immunol Today* 13, 265-270.

Mantovani, A., Bussolino, F., and Dejana, E. (1992b). Cytokine regulation of endothelial cell function. *FASEB J* 6, 2591-2599.

Mantovani, A., Bussolino, F., and Introna, M. (1997). Cytokine regulation of endothelial cell function: from molecular level to the bedside. *Immunol Today* 18, 231-240.

Melaiu, Ombretta, Federica Gemignani, and Stefano Landi. "The Genetic Susceptibility in the Development of Malignant Pleural Mesothelioma." *Journal of Thoracic Disease* 10, no. Suppl 2 (January 2018): S246–52.

Meng, Qingsong, Weixue Sun, John Jiang, Nicole M. Fletcher, Michael P. Diamond, and Ghassan M. Saed. "Identification of Common Mechanisms between Endometriosis and Ovarian Cancer." *Journal of Assisted Reproduction and Genetics* 28 (2011): 917–23.

Merritt, Melissa A., Adèle C. Green, Christina M. Nagle, Penelope M. Webb, and Australian Cancer Study (Ovarian Cancer) and Australian Ovarian Cancer Study Group. "Talcum Powder, Chronic Pelvic Inflammation and NSAIDs in Relation to Risk of Epithelial Ovarian Cancer." *Int. J. Cancer* 122, No. 1 (2008): 170–76.

Merritt, M.A., Green, A.C., Nagle, C.M., Webb, P.M., Australian Cancer Study (Ovarian Cancer) and Australian Ovarian Cancer Study Group. Talcum powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer. *Int. J. Cancer*. (2008)

122:170-176.

Mills, P.K., Riordan, D.G., Cress, R.D., and Young, H.A. (2004). Perineal talc exposure and epithelial ovarian cancer risk in the Central Valley of California. *Int J Cancer* 112, 458-464.

Milne, R. L., and A. C. Antoniou. "Genetic Modifiers of Cancer Risk for BRCA1 and BRCA2 Mutation Carriers." *Annals of Oncology: Official Journal of the European Society for Medical Oncology* 22 Suppl 1 (January 2011): i11-17.

Milne, Roger L., and Antonis C. Antoniou. "Modifiers of Breast and Ovarian Cancer Risks for BRCA1 and BRCA2 Mutation Carriers." *Endocrine-Related Cancer* 23, no. 10 (2016): T69-84. <https://doi.org/10.1530/ERC-16-0277>.

Modan, B., Hartge, P., Hirsh-Yechezkel, G., Chetrit, A., Lubin, F., Beller, U., Ben-Baruch, G., Fishman, A., Menczer, J., Struewing, J.P., *et al.* (2001). Parity, oral contraceptives, and the risk of ovarian cancer among carriers and noncarriers of a BRCA1 or BRCA2 mutation. *N Engl J Med* 345, 235-240.

Moon, Min Chaul, Jung Duck Park, Byung Soon Choi, So Young Park, Dong Won Kim, Yong Hyun Chung, Naomi Hisanaga, and Il Je Yu. "Risk Assessment of Baby Powder Exposure through Inhalation." *Toxicological Research* 27, no. 3 (September 2011): 137-41.

Moorman, P. G., R. T. Palmieri, L. Akushevich, A. Berchuck, and J. M. Schildkraut. "Ovarian Cancer Risk Factors in African-American and White Women." *Am J Epidemiol* 170, No. 5 (September 1, 2009): 598-606.

Mor, G., Yin, G., Chefetz, I., Yang, Y., and Alvero, A. (2011). Ovarian cancer stem cells and inflammation. *Cancer Biol Ther* 11, 708-713.

Mostafa, S. A., C. B. Barger, R. W. Flower, N. B. Rosenshein, T. H. Parmley, and J. D. Woodruff. "Foreign Body Granulomas in Normal Ovaries." *Obstetrics and Gynecology* 66, no. 5 (November 1985): 701-2.

Muscat, J. E., and M. S. Huncharek. "Causation and Disease: Biomedical Science in Toxic Tort Litigation." *Journal of Occupational Medicine.: Official Publication of the Industrial Medical Association* 31, no. 12 (December 1989): 997-1002.

Nadler, Diana L., and Igor G. Zurbenko. "Estimating Cancer Latency Times Using a Weibull Model," 2014, 8.

Narod, S.A., Risch, H., Moslehi, R., Dorum, A., Neuhausen, S., Olsson, H., Provencher, D., Radice, P., Evans, G., Bishop, S., *et al.* (1998). Oral contraceptives and the risk of hereditary ovarian cancer. Hereditary Ovarian Cancer Clinical Study Group. *N Engl J Med* 339, 424-428.

National Toxicology Program. Toxicology and carcinogenesis studies of talc (CAS No. 14807-96-6) in F344/N rats and B6C3F₁ mice (Inhalation studies); 1993. Report No. NTP TR 421; NIH Publication No. 93-3152.

Nelson, Heather H., and Karl T. Kelsey. "The Molecular Epidemiology of Asbestos and Tobacco in Lung Cancer." *Oncogene* 21, no. 48 (October 21, 2002): 7284–88.

Ness, R. B., and C. Cottreau. "Possible Role of Ovarian Epithelial Inflammation in Ovarian Cancer." *JNCI Journal of the National Cancer Institute* 91, no. 17 (September 1, 1999): 1459–67. <https://doi.org/10.1093/jnci/91.17.1459>.

Ness, Roberta B., Jeane Ann Grisso, Carrie Cottreau, Jennifer Klapper, Ron Vergona, James E. Wheeler, Mark Morgan, and James J. Schlesselman. "Factors Related to Inflammation of the Ovarian Epithelium and Risk of Ovarian Cancer." *Epidemiology* 11, No. 2 (2000): 111–17.

Newhouse, M. L., G. Berry, J. C. Wagner, and M. E. Turok. "A Study of the Mortality of Female Asbestos Workers." *British Journal of Industrial Medicine* 29, no. 2 (April 1972): 134–41.

NIOSH - CDC – Occupational Cancer – Carcinogen List, May 2012

"NIOSH 2011 Current Intelligence Bulletin No. 62," 2011.

NIOSH. "Asbestos Fibers and Other Elongated Mineral Particles: State of the Science and Roadmap for Research (Revised Draft)," January 2009.

NIOSH. "Fiber Exposure during Use of Baby Powders, Report No. IWS-36-6.," July 1972..

"NTP Toxicology and Carcinogenesis Studies of Talc (CAS No. 14807-96-6)(NonAsbestiform) in F344/N.Rats and B6C3F1 Mice (Inhalation Studies)," 1993.

Nunes, S.C., and Serpa, J. (2018). Glutathione in Ovarian Cancer: A Double-Edged Sword. *Int J Mol Sci* 19.

Oberdörster, Günter, Eva Oberdörster, and Jan Oberdörster. "Nanotoxicology: An Emerging Discipline Evolving from Studies of Ultrafine Particles." *Environmental Health Perspectives* 113, no. 7 (July 2005): 823–39.

Paoletti, L., Caiazza, S., Donelli, G., and Pocchiari, F. (1984). Evaluation by electron microscopy techniques of asbestos contamination in industrial, cosmetic, and pharmaceutical talcs. *Regul Toxicol Pharmacol* 4, 222-235.

Paluch-Shimon, S., Cardoso, F., Sessa, C., Balmana, J., Cardoso, M.J., Gilbert, F., Senkus, E., and Committee, E.G. (2016). Prevention and screening in BRCA mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO Clinical Practice Guidelines for cancer prevention and screening. *Ann Oncol* 27, v103-v110.

Paoletti, L., Caiazza, S., Donelli, G., and Pocchiari, F. (1984). Evaluation by electron microscopy techniques of asbestos contamination in industrial, cosmetic, and pharmaceutical talcs. *Regul Toxicol Pharmacol* 4, 222-235.

Pardoll, D.M. (2002). Spinning molecular immunology into successful immunotherapy. *Nat Rev Immunol* 2, 227-238.

Park, Hyo K., Joellen M. Schildkraut, Anthony J. Alberg, Elisa V. Bandera, Jill S. Barnholtz-Sloan, Melissa Bondy, Sydnee Crankshaw, et al. "Benign Gynecologic Conditions Are Associated with Ovarian Cancer Risk in African-American Women: A Case-Control Study." *Cancer Causes & Control*, September 29, 2018.

Parmley, T. H., and J. D. Woodruff. "The Ovarian Mesothelioma." *American Journal of Obstetrics and Gynecology* 120, no. 2 (September 15, 1974): 234-41

Peshkin, B., and et al. "Genetic Counseling and Testing for Hereditary Breast and Ovarian Cancer - UpToDate," 2018.

https://www.uptodate.com/contents/genetic-counseling-and-testing-for-hereditary-breast-and-ovarian-cancer?search=Genetic%20counseling%20and%20testing%20for%20hereditary%20breast%20and%20ovarian%20cancer&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1.

———. "Overview of Hereditary Breast and Ovarian Cancer Syndromes - UpToDate," 2018.

https://www.uptodate.com/contents/overview-of-hereditary-breast-and-ovarian-cancer-syndromes?search=Overview%20of%20hereditary%20breast%20and%20ovarian%20cancer%20syndrome&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1.

———. "Prevalence of BRCA1 and BRCA2 Mutations and Associated Cancer Risks - UpToDate," 2018.

https://www.uptodate.com/contents/prevalence-of-brca1-and-brca2-mutations-and-associated-cancer-risks?search=prevalence-of-brca1-and-brca2-mu%E2%80%A6search_result%26selectedTitle%3D1~73%26usage_type%3Ddefault%26display_rank%3D1&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2.

Pejovic, T., and Nezhat, F. (2011). Missing link: inflammation and ovarian cancer. *Lancet Oncol* 12, 833-834.

Penninkilampi, Ross and Guy D. Eslick. "Perineal Talc Use and Ovarian Cancer: A Systematic Review and Meta-Analysis." *Epidemiology* 29, No. 1 (January 2018): 41-49.

Phillips, J. C., P. J. Young, K. Hardy, and S. D. Gangolli. "Studies on the Absorption and Disposition of 3H-Labelled Talc in the Rat, Mouse, Guinea-Pig and Rabbit." *Food and Cosmetics Toxicology* 16, no. 2 (April 1978): 161-63.

Pinto, Mauricio, Carlos Balmaceda, Maria L. Bravo, Sumie Kato, Alejandra Villarroel, et al. "Patient Inflammatory Status and CD4+/CD8+ Intraepithelial Tumor Lymphocyte Infiltration are Predictors of Outcomes in High-Grade Serous Ovarian Cancer." *Gynecologic Oncology* (2018).

Pira, E, C Pelucchi, L Buffoni, A Palmas, M Turbiglio, E Negri, P G Piolatto, and C La Vecchia. "Cancer Mortality in a Cohort of Asbestos Textile Workers." *British Journal of Cancer* 92, no. 3 (February 2005): 580-86. <https://doi.org/10.1038/sj.bjc.6602240>.

Pira, Enrico, Canzio Romano, Francesco S. Violante, Andrea Farioli, Giovanna Spatari, Carlo La

Vecchia, and Paolo Boffetta. "Updated Mortality Study of a Cohort of Asbestos Textile Workers." *Cancer Medicine* 5, no. 9 (2016): 2623–28.

Pukkala, Eero, Jan Ivar Martinsen, Elsebeth Lynge, Holmfridur Kolbrun Gunnarsdottir, Pär Sparén, Laufey Tryggvadottir, Elisabete Weiderpass, and Kristina Kjaerheim. "Occupation and Cancer - Follow-up of 15 Million People in Five Nordic Countries." *Acta Oncologica (Stockholm, Sweden)* 48, no. 5 (2009): 646–790.

Purdie, David, Adèle Green, Christopher Bain, Victor Siskind, Bruce Ward, Neville Hacker, Michael Quinn, Gordon Wright, Peter Russell, and Beatrice Susil. "Reproductive and Other Factors and Risk of Epithelial Ovarian Cancer: An Australian Case-Control Study." *International Journal of Cancer* 62, No. 6 (September 15, 1995): 678–84.

Radic, I, I Vucak, J Milosevic, A Marusic, S Vukicevic, and M Marusic. "Immunosuppression Induced by Talc Granulomatosis in the Rat." *Clinical and Experimental Immunology* 73, no. 2 (August 1988): 316–21.

Ramus, S.J., Vierkant, R.A., Johnatty, S.E., Pike, M.C., Van Den Berg, D.J., Wu, A.H., Pearce, C.L., Menon, U., Gentry-Maharaj, A., Gayther, S.A., *et al.* (2008). Consortium analysis of 7 candidate SNPs for ovarian cancer. *Int J Cancer* 123, 380-388.

Rebbeck, T.R., Mitra, N, Wan, F., Sinilnikova, O.M., Healey, S., McGuffog, L., Mazoyer, S., Chenevix-Trench, G., Easton, D.F., Antoniou, A.C., Nathanson, K.L., the CIMBA Consortium. Association of type and location of BRCA1 and BRCA2 mutations with risk of breast and ovarian cancer. *JAMA*. (2015). April 7; 313(13):1347-1361.

Reid, B.M., Permeth, J.B., Sellers, T.A. Epidemiology of ovarian cancer: a review. *Cancer Med Biol.* (February 2017) Vol 14, No 1.

Reid, A., J. Heyworth, N. de Klerk, and A. W. Musk. "The Mortality of Women Exposed Environmentally and Domestically to Blue Asbestos at Wittenoom, Western Australia." *Occupational and Environmental Medicine* 65, no. 11 (November 2008): 743–49.
<https://doi.org/10.1136/oem.2007.035782>.

Reid, A., N. de Klerk, and A. W. Musk. "Does Exposure to Asbestos Cause Ovarian Cancer? A Systematic Literature Review and Meta-Analysis." *Cancer Epidemiology Biomarkers & Prevention* 20, no. 7 (July 1, 2011): 1287–95.

Reid, Alison, Amanda Segal, Jane S. Heyworth, Nicholas H. de Klerk, and Arthur W. Musk. "Gynecologic and Breast Cancers in Women after Exposure to Blue Asbestos at Wittenoom." *Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology* 18, no. 1 (January 2009): 140–47.

Reuter, Simone, Subash C. Gupta, Madan M. Chaturvedi, and Bharat B. Aggarwal. "Oxidative Stress, Inflammation, and Cancer: How Are They Linked?" *Free Radical Biology and Medicine* 49, no. 11 (December 1, 2010): 1603–16.

Ring, Kari L., Christine Garcia, Martha H. Thomas, and Susan C. Modesitt. "Current and Future Role of Genetic Screening in Gynecologic Malignancies." *American Journal of Obstetrics and Gynecology* 217, no. 5 (2017): 512–21.

Rohl, A. N. "Asbestos in Talc." *Environmental Health Perspectives* 9 (December 1974): 129–32.

Rohl, A. N., A. M. Langer, I. J. Selikoff, A. Tordini, R. Klimentidis, D. R. Bowes, and D. L. Skinner. "Consumer Talcums and Powders: Mineral and Chemical Characterization." *Journal of Toxicology and Environmental Health* 2, no. 2 (November 1976): 255–84.

Rosenblatt, Karin A., Moyses Szklo, and Neil B. Rosenshein. "Mineral Fiber Exposure and the Development of Ovarian Cancer." *Gynecologic Oncology* 45, No. 1 (April 1992): 20–25.

Rosenblatt, Karin A., Noel S. Weiss, Kara L. Cushing-Haugen, Kristine G. Wicklund, and Mary Anne Rossing. "Genital Powder Exposure and the Risk of Epithelial Ovarian Cancer." *Cancer Causes Control* 22, No. 5 (May 2011): 737–42.

Rösler, J. A., H. J. Woitowitz, H. J. Lange, R. H. Woitowitz, K. Ulm, and K. Rödelberger. "Mortality Rates in a Female Cohort Following Asbestos Exposure in Germany." *Journal of Occupational Medicine: Official Publication of the Industrial Medical Association* 36, no. 8 (August 1994): 889–93.

Ross, M. "Geology, Asbestos, and Health." *Environmental Health Perspectives* 9 (December 1974): 123–24.

Saed, Ghassan M., Rouba Ali-Fehmi, Zhong L. Jiang, Nicole M. Fletcher, Michael P. Diamond, Husam M. Abu-Soud, and Adnan R. Munkarah. "Myeloperoxidase Serves as a Redox Switch That Regulates Apoptosis in Epithelial Ovarian Cancer." *Gynecologic Oncology* 116, no. 2 (February 2010): 276–81. <https://doi.org/10.1016/j.ygyno.2009.11.004>.

Saed, G.M., Diamond, M.P., and Fletcher, N.M. (2017). Updates of the role of oxidative stress in the pathogenesis of ovarian cancer. *Gynecol Oncol* 145, 595-602.

Saed, G.M., Morris, R.T., and Fletcher, N.M. (2018). New Insights into the Pathogenesis of Ovarian Cancer: Oxidative Stress. In *Ovarian Cancer-From Pathogenesis to Treatment* (IntechOpen).

Savant, Sudha S., Shruthi Sriramkumar and Heather M. O'Hagan. "The Role of Inflammation and Inflammatory Mediators in the Development, Progression, Metastasis, and Chemoresistance of Epithelial Ovarian Cancer." *Cancers* 10, No. 251 (2018).

Schildkraut, J. M., S. E. Abbott, A. J. Alberg, E. V. Bandera, J. S. Barnholtz-Sloan, M. L. Bondy, M. L. Cote, et al. "Association between Body Powder Use and Ovarian Cancer: The African American Cancer Epidemiology Study (AACES)." *Cancer Epidemiol Biomarkers Prev.* 25, No. 10 (October 1, 2016): 1411–17.

Sellers, T.A., Huang, Y., Cunningham, J., Goode, E.L., Sutphen, R., Vierkant, R.A., Kelemen, L.E., Fredericksen, Z.S., Liebow, M., Pankratz, V.S., *et al.* (2008). Association of single nucleotide polymorphisms in glycosylation genes with risk of epithelial ovarian cancer. *Cancer Epidemiol Biomarkers Prev* 17, 397-404.

Shan, W., and Liu, J. (2009). Inflammation: a hidden path to breaking the spell of ovarian cancer. *Cell Cycle* 8, 3107-3111.

Shen, H., Fridley, B.L., Song, H., Lawrenson, K., Cunningham, J.M., Ramus, S.J., Cicek, M.S., Tyrer, J., Stram, D., Larson, M.C., *et al.* (2013). Epigenetic analysis leads to identification of HNF1B as a subtype-specific susceptibility gene for ovarian cancer. *Nat Commun* 4, 1628.

Sellers, T.A., Huang, Y., Cunningham, J., Goode, E.L., Sutphen, R., Vierkant, R.A., Kelemen, L.E., Fredericksen, Z.S., Liebow, M., Pankratz, V.S., *et al.* (2008). Association of single nucleotide polymorphisms in glycosylation genes with risk of epithelial ovarian cancer. *Cancer Epidemiol Biomarkers Prev* 17, 397-404.

Shukla, A., MacPherson, M.B., Hillegass, J., Ramos-Nino, M.E., Alexeeva, V., Vacek, P.M., Bond, J.P., Pass, H.I., Steele, C., Mossman, B.T. Alterations in gene expression in human mesothelial cells correlate with mineral pathogenicity. *Am J Respir Cell Mol Biol.* (2009). 41:114-123.

Shushan, Asher, Orn Pnlticl, and JoRe Iscovich. "Human Menopausal Gonadotropin and the Risk of Epithelial Ovarian Cancer." *Gynecol-Endocrin* 65, No. 1 (January 1996).

Siegel, R.L., Miller, K.D., and Jemal, A. (2015). Cancer statistics, 2015. *CA Cancer J Clin* 65, 5-29.

Sjösten, A. C. E., H. Ellis, and G. a. B. Edelstam. "Retrograde Migration of Glove Powder in the Human Female Genital Tract." *Human Reproduction* 19, no. 4 (April 1, 2004): 991–95.

Soong, Thing Rinda, Brooke E. Howitt, Alexander Miron, Neil S. Horowitz, Frank Campbell, Colleen M. Feltmate, Michael G. Muto, et al. "Evidence for Lineage Continuity between Early Serous Proliferations (ESPs) in the Fallopian Tube and Disseminated High-Grade Serous Carcinomas." *The Journal of Pathology*, July 25, 2018.

Starita, Lea M., Muhtadi M. Islam, Tapahsama Banerjee, Aleksandra I. Adamovich, Justin Gullingsrud, et al. "A Multiplex Homology-Directed DNA Repair Assay Reveals the Impact of More Than 1,000 BRCA1 Missense Substitution Variants on Protein Function." *American Journal of Human Genetics* 103, (October 4, 2018): 1-11.

Steiling, W., J. F. Almeida, H. Assaf Vandecasteele, S. Gilpin, T. Kawamoto, L. O'Keeffe, G. Pappa, K. Rettinger, H. Rothe, and A. M. Bowden. "Principles for the Safety Evaluation of Cosmetic Powders." *Toxicology Letters*, August 17, 2018.

Steiling, W., M. Bascompta, P. Carthew, G. Catalano, N. Corea, A. D'Haese, P. Jackson, et al. "Principle Considerations for the Risk Assessment of Sprayed Consumer Products." *Toxicology*

Letters 227, no. 1 (May 16, 2014): 41–49.

Stewart, Louise M., Katrina Spilsbury, Susan Jordan, Colin Stewart, C. D’Arcy J. Holman, Aime Powell, Joanne Reekie, and Paul Cohen. “Risk of High-Grade Serous Ovarian Cancer Associated with Pelvic Inflammatory Disease, Parity and Breast Cancer.” *Cancer Epidemiology* 55 (August 2018): 110–16.

Straif, Kurt, Lamia Benbrahim-Tallaa, Robert Baan, Yann Grosse, Béatrice Secretan, Fatiha El Ghissassi, Véronique Bouvard, et al. “A Review of Human Carcinogens—Part C: Metals, Arsenic, Dusts, and Fibres.” *The Lancet Oncology* 10, No. 5 (May 2009): 453–54.

Terry, K. L., S. Karageorgi, Y. B. Shvetsov, M. A. Merritt, G. Lurie, P. J. Thompson, M. E. Carney, et al. “Genital Powder Use and Risk of Ovarian Cancer: A Pooled Analysis of 8,525 Cases and 9,859 Controls.” *Cancer Prev Res* 6, No. 8 (August 2013): 811–21.

Titus-Ernstoff, L., Perez, K., Cramer, D.W., Harlow, B.L., Baron, J.A., and Greenberg, E.R. (2001). Menstrual and reproductive factors in relation to ovarian cancer risk. *Br J Cancer* 84, 714-721.

Torre, L.A., Bray, F., Siegel, R.L., Ferlay, J., Lortet-Tieulent, J., and Jemal, A. (2015). Global cancer statistics, 2012. *CA Cancer J Clin* 65, 87-108.

Trabert, B., R. B. Ness, W.-H. Lo-Ciganic, M. A. Murphy, E. L. Goode, E. M. Poole, L. A. Brinton, et al. “Aspirin, Nonaspirin Nonsteroidal Anti-Inflammatory Drug, and Acetaminophen Use and Risk of Invasive Epithelial Ovarian Cancer: A Pooled Analysis in the Ovarian Cancer Association Consortium.” *J Natl Cancer Inst* 106, No. 2 (February 6, 2014).

Trabert, Britton, Elizabeth M Poole, Emily White, Kala Visvanathan, Hans-Olov Adami, Garnet L Anderson, Theodore M Brasky, et al. “Analgesic Use and Ovarian Cancer Risk: An Analysis in the Ovarian Cancer Cohort Consortium.” *J Natl Cancer Inst*, 111, No. 2 (May 31, 2018).

Tzonou, Anastasia, Argy Polychronopoulou, Chung-cheng Hsieh, Apostolos Rebelakos, Anna Karakatsani and Dimitrios Trichopoulos. “Hair Dyes, Analgesics, Tranquilizers and Perineal Talc Application as Risk Factors for Ovarian Cancer,” *Int. J. Cancer*, 55, (1993): 408-410.

U.S. Environmental Protection Agency (USEPA), “Arsenic, inorganic”, in the Integrated Risk Information System database listing (1995). Available at the USEPA Website:
https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0278_summary

US EPA. “Health Assessment Document for Talc. | National Technical Reports Library - NTIS.” -600/8-91/217, 1992.
<https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/PB92239524.xhtml>.

Vallyathan N.V. and J.E. Craighead, “Pulmonary pathology in workers exposed to nonasbestiform talc”, *Human Pathology* 12(1):28-35 (1981).

Van Gosen, B. S., H.A. Lowers, S.J. Sutley, and C.A. Gent. “Using the Geologic Setting of Talc

Deposits as an Indicator of Amphibole Asbestos Content.” *Environmental Geology* 45, no. 7 (2004): 20.

Vasama-Neuvonen, K., E. Pukkala, H. Paakkulainen, P. Mutanen, E. Weiderpass, P. Boffetta, N. Shen, T. Kauppinen, H. Vainio, and T. Partanen. “Ovarian Cancer and Occupational Exposures in Finland.” *American Journal of Industrial Medicine* 36, no. 1 (July 1999): 83–89.

Venkatesan, Priya. “Possible X Chromosome-Linked Transmission of Ovarian Cancer.” *The Lancet. Oncology* 19, no. 4 (April 2018): e185.

Venter, P. F., and M. Iturralde. “Migration of a Particulate Radioactive Tracer from the Vagina to the Peritoneal Cavity and Ovaries.” *South African Medical Journal = Suid-Afrikaanse Tydskrif Vir Geneeskunde* 55, no. 23 (June 2, 1979): 917–19.

Verdoodt, Freija, Christian Dehlendorff, Søren Friis, and Susanne K. Kjaer. “Non-Aspirin NSAID Use and Ovarian Cancer Mortality.” *Gynecologic Oncology* 150, no. 2 (2018): 331–37.

Virta, RL. “The Phase Relationship of Talc and Amphiboles in a Fibrous Talc Sample.” IH; Report of Investigations, 1985.

Vitonis, A.F., Titus-Ernstoff, L., and Cramer, D.W. (2011). Assessing ovarian cancer risk when considering elective oophorectomy at the time of hysterectomy. *Obstet Gynecol* 117, 1042-1050.

Wang, N.S., Jaurand, M.C., Magne, L., Kheuang, L., Pinchon, M.C., and Bignon, J. (1987). The interactions between asbestos fibers and metaphase chromosomes of rat pleural mesothelial cells in culture. A scanning and transmission electron microscopic study. *Am J Pathol* 126, 343-349.

Wang, Q. (2016) “Cancer predisposition genes: molecular mechanisms and clinical impact on personalized cancer care: examples of Lynch and HBOC syndromes.” *Acta Pharmacologica Sinica* 37:143-149.

Wehner, A.P. (1994). Biological effects of cosmetic talc. *Food Chem Toxicol* 32, 1173-1184.

Wehner, A. P., A. S. Hall, R. E. Weller, E. A. Lepel, and R. E. Schirmer. “Do Particles Translocate from the Vagina to the Oviducts and Beyond?” *Food and Chemical Toxicology: An International Journal Published for the British Industrial Biological Research Association* 23, no. 3 (March 1985): 367–72.

Wehner, A. P., R. E. Weller, and E. A. Lepel. “On Talc Translocation from the Vagina to the Oviducts and Beyond.” *Food and Chemical Toxicology: An International Journal Published for the British Industrial Biological Research Association* 24, no. 4 (April 1986): 329–38.

Wendel, Jillian R. Hufgard, Xiyin Wang and Shannon M. Hawkins. “The Endometriotic Tumor Microenvironment in Ovarian Cancer.” *Cancers* 10, No. 261 (2018).

Werner, I. “Presence of Asbestos in Talc Samples.” *Atenschutzinform* 21, no. 5 (1982).

Whittemore, Alice S, Marion L Wu, Ralphs Paffenbarger, L Sarles, James B Kampert, and S'Tella Grosser. "Personal and Environmental Characteristics Related to Epithelial Ovarian Cancer," *Am J Epidemiol*, 128, No. 6 (1988) 1228-1240.

Wignall, B.K., and A.J. Fox. "Mortality of Female Gas Mask Assemblers." *British Journal of Industrial Medicine* 39, no. 1 (1982): 34–38.

Wong, C. "Perineal Talc Exposure and Subsequent Epithelial Ovarian Cancer: A Case-Control Study." *Obstetrics & Gynecology* 93, No. 3 (March 1999): 372–76.

Woodruff, J. D. "The Pathogenesis of Ovarian Neoplasia." *The Johns Hopkins Medical Journal* 144, no. 4 (April 1979): 117–20.

Wu, A.H., Pearce, C.L., Tseng, C.C., Templeman, C., and Pike, M.C. (2009). Markers of inflammation and risk of ovarian cancer in Los Angeles County. *Int J Cancer* 124, 1409-1415.

Wu, A. H., C. L. Pearce, C.-C. Tseng, and M. C. Pike. "African Americans and Hispanics Remain at Lower Risk of Ovarian Cancer Than Non-Hispanic Whites after Considering Nongenetic Risk Factors and Oophorectomy Rates." *Cancer Epidemiol Biomarkers Prev* 24, No. 7 (July 2015): 1094–1100.

Yegles, M., Saint-Etienne, L., Renier, A., Janson, X., and Jaurand, M.C. (1993). Induction of metaphase and anaphase/telophase abnormalities by asbestos fibers in rat pleural mesothelial cells in vitro. *Am J Respir Cell Mol Biol* 9, 186-191.

Yilmaz, Ercan, Mehmet Gul, Rauf Melekoglu, Isil Koleli. "Immunohistochemical Analysis of Nuclear Factor Kappa Beta Expression in Etiopathogenesis of Ovarian Tumors." *Acta Cir Bras.* 33, No. 7 (2018): 641-650.

Zazenski, R., W. H. Ashton, D. Briggs, M. Chudkowski, J. W. Kelse, L. MacEachern, E. F. McCarthy, M. A. Nordhauser, M. T. Roddy, and N. M. Teetsel. "Talc: Occurrence, Characterization, and Consumer Applications." *Regulatory Toxicology and Pharmacology: RTP* 21, no. 2 (April 1995): 218–29.

Zervomanoklakis, I, H.W. Ott, D Hadziomerovic, V. Mattle, B.E. Seeber, I. Virgolini, D. Heute, S. Kissler, G. Leyendecker, and L. Wildt. "Physiology of Upward Transport in the Human Female Genital Tract." *Annals of New York Academy of Sciences* 1101, no. 1 (2007): 1–20.

Depositions

Deposition of Alice M. Blount in Gail Lucille Ingham, et al. v. Johnson & Johnson, et al.

Depositions of John Hopkins (Aug 16 and 17, 2018; Oct 26, 2018; Nov 5, 2018)

Deposition of Julie Pier (Sept. 12 and 13, 2018)

Expert Reports

Expert Report of Michael Crowley, PhD (Nov. 15, 2018)

Expert Report of William E. Longo, PhD and Mark W. Rigler PhD (Nov. 14, 2018)

Expert Report of William E. Longo, PhD and Mark W. Rigler PhD. Analysis of J&J Baby Powder & Valiant Shower to Shower Talc Products for Amphibole (Tremolite) Asbestos Expert Report. August 2, 2017.

Expert Report of William E. Longo, PhD and Mark W. Rigler PhD. TEM Analysis of Historical 1978 Johnson's Baby Powder Sample for Amphibole Asbestos . February 16, 2018.

Documents Produced

JNJ 000018679-90

JNJTALC000864509-732

Exhibit 34

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Page 1

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE: JOHNSON &)
JOHNSON TALCUM POWDER)
PRODUCTS MARKETING)
SALES PRACTICES AND) MDL 16-2738
PRODUCT LIABILITY) (FLW)(LHG)
LITIGATION)
_____)
THIS DOCUMENT)
PERTAINS TO ALL CASES)

WEDNESDAY, DECEMBER 19, 2018

CONFIDENTIAL - PURSUANT TO PROTECTIVE ORDER

- - -

Videotaped deposition of Laura Plunkett, Ph.D., DABT, held at the Four Seasons Hotel, 999 North 2nd Street, St. Louis, Missouri, commencing at 9:12 a.m., on the above date, before Carrie A. Campbell, Registered Diplomate Reporter, Certified Realtime Reporter, Illinois, California & Texas Certified Shorthand Reporter, Missouri & Kansas Certified Court Reporter.

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19

V I D E O G R A P H E R :

20 JACOB ARNDT,
21 Golkow Litigation Services

- - -

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23
24
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Page 5

1 8 "Weight of Evidence: General 211
 Principles and Current Applications
2 at Health Canada"
3 (Exhibits attached to the deposition.)

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1 VIDEOGRAPHER: We are now on
2 the record.

3 My name is Jacob Arndt. I'm a
4 videographer for Golkow Litigation
5 Services.

6 Today's date is December 19,
7 2018, and the time is 9:12 a.m.

8 This deposition is being held
9 in St. Louis, Missouri, In Re: Johnson
10 & Johnson Products Marketing Sales
11 Practices, for the United States
12 District Court for the District of
13 New Jersey.

14 The deponent is Dr. Laura
15 Plunkett.

16 Will counsel please identify
17 themselves?

18 MR. MEADOWS: Ted Meadows for
19 plaintiffs.

20 MS. PARFITT: Michelle Parfitt
21 for the plaintiffs.

22 MR. BEATTIE: Ryan Beattie for
23 plaintiffs.

24 MR. TISI: Chris Tisi for
25 plaintiffs.

1 MR. GOLOMB: Richard Golomb for
2 plaintiffs.

3 MR. LOCKE: Tom Locke for the
4 Personal Care Products Council.

5 MS. TINSLEY: Caroline Tinsley
6 for PTI Union, LLC, and PTI Royston,
7 LLC.

8 MR. SULLIVAN: Ryan Sullivan
9 for Imerys.

10 MS. BOCKUS: Jane Bockus for
11 Imerys.

12 MR. SMITH: William Smith for
13 Johnson & Johnson.

14 MS. BRANSCOME: Kimberly
15 Branscome for Johnson & Johnson.

16 VIDEOGRAPHER: Thank you.

17 The court reporter is Carrie
18 Campbell and will now swear in the
19 witness.

20 LAURA PLUNKETT, Ph.D., DABT,
21 of lawful age, having been first duly sworn
22 to tell the truth, the whole truth and
23 nothing but the truth, deposes and says on
24 behalf of the Defendant Johnson & Johnson, as
25 follows:

1 DIRECT EXAMINATION

2 QUESTIONS BY MS. BRANSCOME:

3 Q. All right. Good morning,
4 Dr. Plunkett. I introduced myself right
5 before we started, but my name is Kimberly
6 Branscome, and I am here on behalf of Johnson
7 & Johnson.

8 Is it your understanding today
9 that you are giving your deposition for the
10 purpose of a Daubert analysis in the MDL
11 related to Johnson's baby powder?

12 A. That's my understanding, yes.
13 (Plunkett Exhibit 1 marked for
14 identification.)

15 QUESTIONS BY MS. BRANSCOME:

16 Q. I want to start by handing you
17 what I will mark as Plunkett Deposition
18 Exhibit 1.

19 Do you recognize the document
20 that I just handed you?

21 A. Yes.

22 Q. Okay. Have you seen this
23 document before?

24 A. Yes.

25 Q. All right. When was this

1 document provided to you?

2 A. Either earlier this -- this
3 week or late last week. I don't recall if it
4 was Friday or Monday.

5 Q. Okay. For the purposes of the
6 record, could you just identify what the
7 document is that I just handed you as
8 Plunkett Deposition Exhibit Number 1?

9 A. It's a notice of oral and
10 videotaped deposition for myself, dated -- I
11 don't see the date, but probably on the very
12 last -- do you need that or just -- is that
13 enough of an identification?

14 Q. That's all right.

15 Now, contained within the
16 deposition notice there is a reference to a
17 request for materials that are identified in
18 more detail in Schedule A.

19 Do you see that?

20 A. Yes.

21 Q. Have you reviewed Schedule A?

22 A. Yes.

23 Q. Did you bring any documents
24 with you in response to the request in
25 Schedule A?

1 A. The only thing that I believe
2 that I had to bring that had not already been
3 provided was additional billing since the
4 time of my last deposition.

5 Q. Okay. And is it my
6 understanding that the documentation related
7 to additional billing that you have done
8 since your prior deposition was produced
9 yesterday at the deposition in the Forrest
10 case?

11 A. That's correct.

12 Q. All right. And the information
13 contained in the documents produced at the
14 Forrest deposition yesterday, do those
15 contain an up-to-date record of the billing
16 that you have submitted for your work in
17 connection with the litigation against
18 Johnson & Johnson?

19 A. Yes, with the understanding
20 that I haven't submitted a bill for December
21 yet.

22 Q. Okay. How much time have you
23 spent working in connection with your
24 opinions in the case against Johnson &
25 Johnson related to its baby powder in the

1 month of December?

2 A. So I'm -- on all the cases that
3 I am involved in that are pending, not just
4 this deposition?

5 Q. I'll ask first all cases and
6 then we'll narrow it to the deposition.

7 A. So in all --

8 Q. I mean to the MDL, I'm sorry.

9 A. Okay. So in all cases this
10 month, probably eight hours so far, maybe
11 ten.

12 Q. Does that include the time that
13 you've spent attending deposition?

14 A. No, that's not including
15 yesterday's deposition time. I apologize. I
16 forgot about that.

17 Q. And how much of the eight to
18 ten hours that you have spent this month
19 working on these cases against Johnson &
20 Johnson, setting aside the time you spent in
21 deposition yesterday, relate to the MDL
22 specifically?

23 A. So it will probably be
24 billed -- it will be one bill for the
25 preparation time because the prep overlapped,

1 but I'll bill separately for the time I spent
2 yesterday right before the deposition and
3 then at the deposition, so...

4 Q. What did you do to prepare for
5 your deposition today?

6 A. I reviewed my reports, the
7 three reports that I filed in the litigation.
8 I had a meeting with attorneys on Monday, and
9 then we had a short meeting yesterday evening
10 because some attorneys arrived that were not
11 here on Monday.

12 And essentially went through
13 some of the documents that -- went through
14 some of the documents that I had cited in the
15 report in certain paragraphs, just to refresh
16 my memory of what they were. So if you want
17 me to tell you which paragraphs, I can do
18 that.

19 Q. I will in just a moment. Okay.

20 A. Want me to repeat that? I'm
21 sorry.

22 Q. That's all right.

23 Dr. Plunkett, you referenced
24 the fact that you reviewed specific
25 paragraphs of your expert reports in

1 preparation for today's deposition.

2 Could you identify those
3 paragraphs for me?

4 And it's helpful to you, we can
5 go ahead and mark your three expert reports,
6 if you're referring to all three.

7 A. I'm going to refer just to the
8 MDL report because that's what we're here to
9 talk about. I mean, if you want to talk
10 about what I did to get ready for yesterday
11 separately or --

12 MR. MEADOWS: Might be helpful
13 to go ahead and mark them.

14 MS. BRANSCOME: Why don't we go
15 ahead and just mark the three reports,
16 and then we can walk through.

17 (Plunkett Exhibits 2, 3 and 4
18 marked for identification.)

19 QUESTIONS BY MS. BRANSCOME:

20 Q. So, Dr. Plunkett, do you have a
21 copy of your three reports in front of you?

22 A. Yes, I do.

23 Q. Do those contain any markings,
24 highlightings or flags?

25 A. No, they don't.

1 Q. Okay. Do you mind if we mark
2 your copies as the official records?

3 A. No, that's fine.

4 Q. So we will mark -- well, let's
5 do this in chronological order. So I am
6 marking as Plunkett Deposition Exhibit
7 Number 2 the expert report of Dr. Plunkett
8 dated October 5, 2016.

9 Could you confirm,
10 Dr. Plunkett, that that's what I marked as
11 Deposition Exhibit Number 2?

12 A. Yes, it is.

13 Q. And then we will mark as
14 Deposition Exhibit Number 3 supplemental
15 expert report of Dr. Laura Plunkett dated
16 August 29, 2018.

17 Dr. Plunkett, could you confirm
18 that I marked that as Exhibit Number 3?

19 A. Yes, that's correct.

20 Q. And then Exhibit Number 4, we
21 will mark the expert report dated
22 November 16, 2018, by Dr. Plunkett that was
23 produced in the MDL.

24 Could you confirm that I marked
25 that as Deposition Exhibit Number 4?

1 A. Yes, that's correct.

2 Q. All right. And so now back to
3 the question of you referenced the fact that
4 you looked at specific paragraphs of your
5 expert report in preparation for today's
6 deposition. If you could, using Deposition
7 Exhibit Number 4, identify which paragraphs
8 you looked at specifically in preparation for
9 the deposition.

10 A. So it wasn't the paragraphs.
11 There were certain documents in paragraphs,
12 so that's what I was referring to, so...
13 So starting in paragraph 38
14 where I'm talking about sort of the timeline
15 of information about human health hazards and
16 talc dust. So I just went back and refreshed
17 on a few of the older papers.

18 I looked again at the patent
19 documents that are cited in the first bullet.

20 I looked again at a paper by
21 Eberl, 1948, which is in the last bullet.
22 The patent documents are also there as well.

23 And that -- so that would be
24 all I pulled in that paragraph.

25 I believe that those documents

1 are also cited in paragraph 39 as well, some
2 of those same ones that are...

3 And then in Section 5 of my
4 report where I'm talking about exposure, I
5 looked again at Parmley and Woodruff. I
6 looked again at Vetner and Iturrulde and Egli
7 and Newton last night.

8 And the only other thing I
9 looked at is not cited in this report because
10 it came out after the report was filed, and
11 that was -- and I did bring a copy of that.
12 That was the risk assessment that was done in
13 Canada. Some people refer to it as -- by the
14 first author's last name, Taher, T-a-h-e-r.
15 And I may be pronouncing that wrong, but...

16 (Plunkett Exhibit 5 marked for
17 identification.)

18 QUESTIONS BY MS. BRANSCOME:

19 Q. All right. And I see that you
20 brought a copy of that document with you.
21 Just for the purposes of the record, let's
22 mark that as Plunkett Deposition Exhibit
23 Number 5.

24 Are there any markings,
25 highlightings or notations on that document?

1 A. No, there's not.

2 And then the other document I
3 looked at that was not cited in the report,
4 there is a printout from the government of
5 Canada website that talks about some
6 statements on talc, and so I printed that out
7 as well. This was published at the same time
8 that the risk assessment was published.

9 (Plunkett Exhibit 6 marked for
10 identification.)

11 QUESTIONS BY MS. BRANSCOME:

12 Q. All right. We'll mark that for
13 purposes of the record as Plunkett Deposition
14 Exhibit Number 6. We might come back to
15 those documents.

16 So returning briefly to the
17 deposition notice and the requests in
18 Schedule A, the billing information you
19 produced yesterday and then we just discussed
20 additional information with respect to that,
21 are there any other documents that you have
22 in your possession that are responsive to
23 requests identified in Schedule A that have
24 not been produced?

25 A. I don't believe so, no.

1 Everything -- I do believe that there were
2 some objections filed to this, so there's
3 some things that I did not provide based on
4 that.

5 Some of the things I don't
6 have, too. I think you asked for -- maybe
7 you didn't ask for that. Usually people ask
8 for copies of old depositions, and I don't
9 keep those. And maybe you didn't ask for
10 that, but that's usually a request.

11 Let me see.

12 Q. Okay. Now, you mentioned that
13 you met with attorneys on Monday. And who
14 was present at that meeting?

15 A. So on Monday it was
16 Mr. Meadows, sitting here. Ms. Tucker,
17 Mr. Beattie, were at the meeting on Monday.

18 Q. All right. And how long did
19 that meeting last?

20 A. Probably six hours, I guess,
21 six hours with them, and then I also did some
22 other work on my own, but...

23 Q. Okay. And then you mentioned
24 that you had another meeting last night.

25 Who was present at that

1 meeting?

2 A. So that was probably about an
3 hour, and that would have been Mr. Tisi -- or
4 maybe two hours. Mr. Tisi joined us
5 yesterday afternoon. And Mr. Golomb, too,
6 I'm sorry.

7 Q. All right. Okay. Now, looking
8 at the three reports that you have produced
9 in the litigation involving Johnson's baby
10 powder, I wanted to get an understanding of
11 how those three reports relate to one
12 another.

13 So you have the first report
14 that you produced that was dated October 5,
15 2016. I believe that was originally produced
16 in the Uhl case; is that correct?

17 A. I'm not sure the name of the
18 first case, but it was in the -- some of the
19 St. Louis cases, yes.

20 Q. All right. And when did you
21 begin work on that report?

22 A. You'd have to look at my
23 billing record, which I know was an exhibit
24 to yesterday's deposition. I believe they
25 started in 2015.

1 Q. All right. And then you
2 produced a supplemental report earlier this
3 year, on August 29, 2018, and that's been
4 marked as Deposition Exhibit Number 3,
5 correct?

6 A. Yes.

7 Q. When did you begin work on the
8 supplemental report that you produced at the
9 end of August in 2018?

10 A. I want to say -- let's see. I
11 want to say sometime in the summer. Maybe as
12 early as May, but I believe May -- May, June
13 time frame of 2018.

14 My billing would reflect that,
15 so, again, we can pull my billing. And I
16 would have called it preparation of the
17 supplemental report in my billing.

18 Q. Okay. Why did you choose to
19 draft a supplemental expert report?

20 A. So over the time I had worked
21 on different trials here in St. Louis
22 particularly, additional documents that were
23 not cited in my original report became
24 reliance materials based on their
25 presentation at trial. So there were enough

1 of those that I thought it was important to
2 add to the original report with additional
3 documents that I had reviewed over time.

4 Since October of 2016 through,
5 let's say, the summer of 2018, there were a
6 variety of additional documents that I had --
7 I had seen.

8 It was also my understanding
9 that during that time period Johnson &
10 Johnson had provided additional documents
11 that weren't provided or available to me in
12 2016, so additional discovery that was now
13 available to look at. So some of this is a
14 matter of additional evidence that wasn't
15 available when I wrote my initial -- my
16 initial report.

17 Q. All right. Now when you say
18 the additional documents became reliance
19 materials in trial, what do you mean by that?

20 A. So additional documents that we
21 refer to in trial that I use to support
22 opinions that weren't necessarily
23 specifically cited within the body of my
24 report or described within the body of my
25 report. They were likely on my larger

1 reliance list, but they weren't things that
2 were cited.

3 In other words, if you look at
4 my original report in -- when I say the body,
5 the paragraphs. I always put a reference
6 list and then I'll have Bates numbers. So
7 during trial, things that were from my larger
8 reliance list that weren't specifically
9 discussed in my report became support for
10 different opinions that -- based on questions
11 at trial.

12 Q. Okay. When you say these were
13 documents that "we" refer to at trial, you're
14 referring to yourself and attorneys
15 representing the plaintiffs?

16 A. Yes, that's correct.

17 Q. Okay. And understanding that
18 the purpose of today's deposition is focused
19 specifically on the MDL, then you produced a
20 report specific to the MDL on November 16,
21 2018, that we've marked as Exhibit 4,
22 correct?

23 A. Yes.

24 Q. When did you begin work on the
25 report that you produced specifically in the

1 MDL?

2 A. Sometime right after -- I would
3 say early fall of 2018, sometime after
4 this -- the supplemental report was filed.
5 Probably right after that.

6 Q. Okay. So is it fair to say
7 that you began work on your MDL report after
8 completing the supplemental expert report
9 that has been marked as Exhibit 3?

10 A. Yes, that's correct.

11 Q. Okay. Who was involved in the
12 drafting of the report that's been identified
13 as Exhibit 4?

14 MR. MEADOWS: Objection. Hang
15 on a second.

16 Are you asking about
17 communications between attorneys and
18 Dr. Plunkett?

19 QUESTIONS BY MS. BRANSCOME:

20 Q. Dr. Plunkett, none of the
21 questions I will ask you here today are
22 intended to elicit information that's
23 protected by the attorney-client privilege.

24 So setting that aside, anything
25 that you understand to be privileged, I can

1 ask who the -- who was involved in the
2 drafting of the report that was produced in
3 the MDL?

4 MR. MEADOWS: Hold on just one
5 second.

6 Ask the question one more time.
7 I want to make sure we're not
8 venturing into attorney work product
9 realm here.

10 QUESTIONS BY MS. BRANSCOME:

11 Q. Dr. Plunkett, do you consider
12 the report that you have issued in the MDL
13 which is identified as Exhibit 4 to be
14 attorney work product?

15 MR. MEADOWS: Objection. Don't
16 answer that. That calls for a legal
17 conclusion, and at this point I'm
18 going to instruct you not to answer
19 questions about how the report came
20 into be.

21 MS. BRANSCOME: Are you
22 instructing her to refuse to answer
23 any questions that involve the
24 development of her expert report?

25 MR. MEADOWS: I'm instructing

1 her not to answer your last question.

2 QUESTIONS BY MS. BRANSCOME:

3 Q. Are you following your
4 attorney's instructions, Dr. Plunkett?

5 A. Yes.

6 MS. BRANSCOME: At this point I
7 would like to go off the record,
8 please.

9 VIDEOGRAPHER: Okay. We are
10 going off the record at 9:30 a.m.
11 (Off the record at 9:30 a.m.)

12 VIDEOGRAPHER: We are back on
13 the record at 9:32 a.m.

14 QUESTIONS BY MS. BRANSCOME:

15 Q. Dr. Plunkett, other than
16 attorneys, if attorneys were involved -- I am
17 not asking questions about that -- were there
18 any individuals who assisted you in preparing
19 the report that has been marked as Exhibit 4?

20 A. There was no one that actually
21 assisted in writing the report. I do -- when
22 I did my literature searches, I had my
23 husband help me retrieve articles that I
24 identified for retrieval, but certainly there
25 was no -- he doesn't participate in the

1 actual review of articles or in drafting of
2 the report. That's all my work.

3 Q. Okay. And when you say that
4 your husband retrieved articles, was this
5 simply -- what information did you provide
6 him in order to enable him to retrieve a
7 particular article?

8 A. So we use a service in Houston
9 called Loansome Doc, which is affiliated with
10 our local medical library system and also
11 with the National Library of medicine and NIH
12 libraries. So I give him an online search
13 that I put into a clipboard. He takes that,
14 makes the request or retrieves -- some of
15 them will be free, and so he'll actually go
16 to the websites for the -- and then put them
17 into a folder for me.

18 So he does that physical part
19 of it through the computer, but he doesn't --
20 he doesn't do the searches or decide which
21 ones to retrieve. I do that.

22 Q. Okay. Did you have any
23 discussions with your husband about the
24 substantive content of the report that's
25 identified as Exhibit 4?

1 A. No.

2 Q. Does he do any evaluation --
3 for example, if you were to provide him a
4 search and it generates multiple documents by
5 a given author, does he identify additional
6 articles that you might want to consider?

7 A. Only -- he has done that, but
8 only with the streams of letters to the
9 editor. So I ask him always if I'm pulling
10 an article. Happens a lot at the New England
11 Journal of Medicine or some of the other
12 medical journals where there's pretty active
13 letter to the editor correspondence that
14 happens.

15 So I always say to him, "If
16 there's any citation to this through the
17 letter to the editor comments, would you
18 please retrieve those," and so he will do
19 that search to look for that.

20 Q. Okay.

21 A. And I'm not sure that that
22 happened in any of these articles, but I'm
23 talking my general process that we use.

24 Q. Okay. In terms of the
25 relationship of the three reports that have

1 been marked as Exhibits 2, 3 and 4 to each
2 other, what is your -- what is your position
3 with respect to opinions that you have stated
4 or language you have used in Exhibits 2 and 3
5 that may not appear in Exhibit 4?

6 A. I don't think I understand what
7 your -- what you mean by my position. Are
8 you asking --

9 MS. PARFITT: And I'll object
10 to that question.

11 THE WITNESS: Are you asking me
12 to describe -- I mean, I could
13 describe for you the overlap. I mean,
14 there's not complete overlap. Is that
15 what you're asking me or --

16 QUESTIONS BY MS. BRANSCOME:

17 Q. I am. Why don't you take a
18 shot at it and then I may narrow my question,
19 but I'm just trying to understand how the
20 reports relate to one another.

21 MR. MEADOWS: Objection.

22 THE WITNESS: So they relate to
23 each other, I would say, based on
24 timing first, because obviously the
25 first report was two years ago, and

1 then many more documents. So that's
2 how the 1 and 2 relate -- or Exhibit 2
3 and 3 relate to each other.

4 In the MDL litigation, I was
5 asked to address very specific topics
6 and things because there's a -- it's a
7 different -- I don't know all of them,
8 but there's a different set of experts
9 that work in different litigations.

10 So my role in the MDL, I
11 believe, is set out based on this
12 report, whereas in the original
13 reports I may have had -- I did have a
14 broader role in some of those cases.

15 QUESTIONS BY MS. BRANSCOME:

16 Q. Okay. Can you describe for me
17 your understanding of your role in the MDL?

18 A. It's my understanding that I
19 have been asked to provide opinions related
20 to the -- generally the toxicology of talcum
21 powder products, including all the individual
22 constituents that make up that product; to
23 look historically back in time about what was
24 known and when about the toxic effects of
25 talc and different constituents within talc.

1 And that was sort of the -- that's been --
2 I consider that sort of the meat of what I've
3 been asked to do.

4 But separate from that, another
5 part important part of my testimony or things
6 I was asked to provide was an overview of the
7 regulatory process for cosmetics and then the
8 information that accumulated scientifically,
9 how that related to what a company is
10 required to do under the regulations in order
11 to provide consumers with appropriate
12 information about the safety of the product.
13 So kind of the regulatory opinions, I guess
14 you want to call it, that area.

15 I have sections on that, and I
16 think you can see that by the different
17 sections in my report where I set out
18 different general topics.

19 And then I was also asked to
20 address some of the issues related to how the
21 information on the safety of talc has been
22 disseminated publicly and also based on my
23 review of different internal company
24 documents, both from Johnson & Johnson -- or
25 from Johnson & Johnson, Imerys, as well as

1 the PCPC, which is the Personal Care Products
2 Council, formerly known as the CTFA, to look
3 at those interactions and how those companies
4 set about to influence the process around the
5 safety assessment of talc over the years. So
6 different activities that happened with
7 respect to the ISRTP meetings in the '90s,
8 with respect to the NTP process at different
9 points in time.

10 The CIR process, I think I
11 cover, and I also talk a little bit about
12 IARC, I believe, as well.

13 So the interactions of the
14 industry with the science and then how that
15 science ends up getting described within --
16 either to regulators or to bodies that are
17 reviewing the science related to the
18 products.

19 Q. You mentioned as one of the
20 categories that you were asked to opine about
21 in the MDL that you were looking to set about
22 the influence that companies may have exerted
23 over the regulatory process or PCPC.

24 When you began that analysis,
25 did you start with the predicate belief that

1 the companies had, in fact, influenced the
2 regulators or PCPC?

3 MR. MEADOWS: Objection.

4 THE WITNESS: Not in my -- not
5 when I first started this process. So
6 that is -- those opinions actually go
7 back into my original report. So
8 that's not something, I don't believe,
9 that was not covered in my original
10 report or even in my supplemental
11 report. I just have different -- some
12 additional documents that I have
13 reviewed.

14 QUESTIONS BY MS. BRANSCOME:

15 Q. Okay.

16 A. And this is something when I
17 first evaluated the case and first started
18 looking at the documents, those are opinions
19 that I had formed based on my review.

20 Certainly by the time I drafted
21 the MDL report, I think if you listened to
22 my -- read my trial testimony, you understand
23 I had those opinions at the time I started
24 writing this report.

25 Q. Now, what I'd like to

1 understand next is, are there -- of the
2 topics that you just identified that you
3 understand that you're offering opinions
4 about in the MDL, which, if any, of those
5 topics are in your view new as compared to
6 the opinions that you have offered that are
7 contained in Exhibits 2 and 3?

8 MS. PARFITT: Objection.

9 THE WITNESS: So I don't think
10 any of the MDL opinions are new.

11 QUESTIONS BY MS. BRANSCOME:

12 Q. Okay.

13 A. I think that they may have --
14 they may -- they may cite to additional
15 documents that haven't been cited to in the
16 first two reports, but I believe there's a
17 significant overlap even on the documents
18 that are cited.

19 Q. And you mentioned that your
20 role in the MDL is more narrow than the role
21 you've served in other cases.

22 What topics have you opined
23 about in other cases that you are not
24 intending to opine about in the MDL?

25 A. So I am not doing general

1 causation in the MDL, although I am indeed
2 providing opinions on certain aspects of the
3 cause and effect relationship such as -- you
4 know, I talk about biologic plausibility,
5 underlying knowledge about different
6 toxicities of the compounds over time, but
7 I'm not doing a full causation analysis in my
8 MDL report, and hopefully you see that when
9 you read the report.

10 Q. So as you sit here today,
11 Dr. Plunkett, you are not intending to offer
12 the opinion in the MDL that Johnson's baby
13 powder causes ovarian cancer; is that
14 correct?

15 A. Not in those words. I think if
16 you read my report, I talk about the
17 fact that Johnson -- it's my opinion that
18 Johnson's baby powder increases the risk of
19 cancer -- ovarian cancer, which is a
20 different assessment than the way you stated
21 it.

22 Q. All right. And it is -- as you
23 sit here today, Dr. Plunkett, it is your
24 understanding that you are not being offered
25 to give a, as you termed it, a general

1 causation opinion in the MDL, correct?

2 A. That's my understanding, yes.

3 Q. Now, you mentioned that the
4 analysis as to whether a substance increases
5 the risk of a particular outcome is different
6 than a causation analysis.

7 Can you explain to me what you
8 meant by that?

9 A. So I discussed this yesterday
10 in my deposition. There's -- there's a
11 process called risk assessment. Sometime --
12 in the area of consumer products you can also
13 refer to it as safety assessment. And then
14 there's the process of what I call general
15 causation analysis, or full causation
16 analysis.

17 So even though the types of
18 information that are considered may overlap
19 between those two, the outcome or the
20 statements or the -- the way you go about
21 assessing the information is a bit different.

22 Q. Explain to me how they're
23 different.

24 A. So in a risk assessment, the
25 process starts with setting out some basic

1 principles of, first, is there a hazard, is
2 the first step. Is there a hazard that would
3 be relevant to human health.

4 Then looking at the data and
5 determining whether that -- that body of data
6 allows you to either quantify risk in some
7 way or to qualitatively shows you that
8 there's a change in risk based on exposure to
9 the product.

10 So your statement may be as
11 simple as there's an increased risk, or you
12 can take data in a risk assessment and do a
13 quantification such as in a -- a cancer risk
14 assessment based on an animal data set. You
15 might actually calculate a cancer potency
16 factor, for example. Those kinds of things.
17 That's another application of risk
18 assessment. Same basic process but focusing
19 just, for example, on one study.

20 My human health risk assessment
21 or safety assessment, like the causation
22 analysis, does look across all kinds of data,
23 but my goal was not to analyze the data under
24 the Hill considerations, which is what I
25 would typically do, in order to go through

1 the process of making that final opinion that
2 indeed baby powder -- exposure to baby powder
3 through genital application is a cause of
4 ovarian cancer in women. That's -- to me,
5 that's a different way to go about thinking
6 about the question that you have to answer.

7 And also the -- some of the
8 data that you evaluate is evaluated a bit
9 differently. So, for example, in my
10 increase -- in my issue of increased risk, I
11 use the epidemiology as supporting evidence,
12 but I'm really focused on -- on -- more on
13 the underlying sort of the biologic
14 information that we have that identifies
15 hazard and risk. So looking at the animal
16 data, the exposure potential for the product,
17 and then using that along with what we know
18 with the human experience to characterize
19 risk.

20 Q. Is there a different level of
21 certainty required to render a causation
22 opinion than to render an opinion that
23 there's an increased risk?

24 A. I don't know that I'd describe
25 it quite that way but -- because to me it's a

1 different process. I certainly have to be
2 just as certain about what I say about risk
3 when I do a risk assessment as I do about --
4 as I do when I'm doing a causation analysis.

5 I don't -- maybe you mean
6 something else, so maybe you can -- I mean,
7 I -- I certainly use the same basic standards
8 in my mind, how I weigh evidence to do the
9 different processes, but I go about them in a
10 little bit different way when I do a risk
11 assessment versus -- versus a causation
12 analysis.

13 Q. In your view, does the strength
14 of the evidence have to be greater in order
15 to determine that an agent causes a disease,
16 for example, than it does simply to say that
17 an agent increases the risk of a particular
18 outcome?

19 MR. MEADOWS: Objection.

20 THE WITNESS: I don't think
21 I've ever thought about it that way.
22 I would say to you that strength --
23 the strength of the association is a
24 consideration under Hill that you
25 apply the epidemiology data mainly, so

1 that is a different consideration
2 under causation than you do -- as you
3 would do it in a risk assessment.

4 But the strength of the
5 evidence, it's still a judgment based
6 on your experience and training as far
7 as whether or not there is enough
8 information to be able to say that you
9 believe that there is -- enough
10 information to say that the risk is
11 increased based on that exposure and
12 those conditions and whatever the
13 toxicity profile of that compound is.

14 QUESTIONS BY MS. BRANSCOME:

15 Q. Okay. We'll get into this more
16 a little bit later, but when you say that a
17 risk is increased, is there a threshold level
18 of increase that you need to see in order to
19 render an opinion in a court of law that an
20 agent increases the risk of a particular
21 outcome?

22 MR. MEADOWS: Objection.

23 THE WITNESS: So I need you to
24 define what you mean by threshold.
25 Are you asking me a specific

1 statistical test you would apply, or
2 what are you asking?

3 QUESTIONS BY MS. BRANSCOME:

4 Q. So understanding that for the
5 most part if you're looking at statistical
6 significance, you're looking whether the
7 confidence interval crosses 1.

8 Are you following?

9 A. Yes, I know that, yeah.

10 Q. All right. And so when you're
11 evaluating, though, whether a particular
12 substance, in this case Johnson's baby
13 powder, increases the risk of an outcome,
14 again, in this case ovarian cancer, would it
15 be sufficient for you if that increase was
16 .01 percent, for example?

17 MR. MEADOWS: Objection.

18 THE WITNESS: That doesn't make
19 sense to me, an increase of .01
20 percent, but maybe I can answer it
21 this way for you based on what you've
22 laid out there.

23 Certainly when I do a risk
24 assessment and I make it -- if I'm
25 going to make the conclusion that I

1 believe that it's my opinion to a
2 reasonable degree of scientific
3 certainty that exposure to baby powder
4 in women increases the risk of cancer,
5 I'm having to rely on -- I do rely on
6 data that allows me to draw
7 conclusions because either there's a
8 statistical significant finding found
9 or the -- there's a consistency among
10 the pattern of the data that shows
11 there's information that fits together
12 consistently. And maybe -- you want
13 me to explain what I mean by that?
14 No?

15 Whereas I think what you're
16 asking is when an epidemiologist
17 applies -- looks at a body of -- in a
18 causation analysis looks at a body --
19 and I do this, too -- looks at a body
20 of epidemiological studies and you
21 weight the studies, obviously you're
22 weighting the studies differently
23 based on whether they have shown
24 statistical significance or not,
25 right?

1 And it isn't that it's a one to
2 one. If you have one positive and one
3 negative, that isn't how you may
4 decide to finally weight that
5 evidence, but certainly you have to
6 consider whether or not what was seen
7 or reported is showing you something
8 reliable -- or you can make a
9 statement reliably about whether or
10 not that finding was biologically
11 significant. And biologically
12 significant would typically be linked
13 to a finding that has statistical
14 significance in an epi study unless
15 the study was not designed to be able
16 to answer the question properly.

17 So -- and I've discussed that a
18 little bit yesterday with Mr. Smith on
19 the issue of power to detect. So
20 that's something you do consider in
21 epi.

22 But, yes, statistical
23 significance certainly goes into your
24 weight of the evidence there.

25

1 QUESTIONS BY MS. BRANSCOME:

2 Q. Okay. You talked about you're
3 intending to offer an opinion with respect to
4 what a company is required to do under the
5 regulations; is that correct?

6 A. Yes.

7 Q. Okay. What regulations are you
8 specifically referring to?

9 A. So cosmetic regulations that
10 exist within -- so it's the entire process as
11 I describe how cosmetic -- what -- are
12 cosmetics subject to regulation by FDA? Yes.
13 What are the types of things that companies
14 have to do before they're marketed, what does
15 the company have to do once the product is on
16 the market, those kinds of things.

17 Q. Have you ever worked directly
18 for any regulatory agency?

19 A. No, I have not.

20 Q. And suffice it to say you have
21 never been in a decision-making position
22 within a regulatory agency, correct?

23 A. That's correct, I have not.

24 Q. Have you ever been in a
25 decision-making position with respect to a

1 company evaluating compliance with FDA
2 regulations with respect to cosmetics?

3 A. Yes.

4 Q. Okay. What is your experience
5 with respect to that?

6 A. So that's -- one of the clients
7 that I currently work for where I am asked to
8 provide input on advertising, promotion and
9 labeling of some of the products and then
10 also some of the ingredients that are being
11 promoted for use to -- to produce cosmetic
12 products. So it's the idea of providing that
13 advice over my understanding of the
14 regulations what can be said and can't be
15 said about certain ingredients.

16 This company is involved in
17 making both ingredients but also some
18 finished products now based on -- it's a
19 large company that owns a lot of little
20 subsidiaries.

21 Q. My question, though,
22 Dr. Plunkett, was, have you ever been in a
23 decision-making position for a company
24 evaluating compliance with FDA regulations
25 with respect to cosmetics?

1 MS. PARFITT: Objection. Asked
2 and answered.

3 THE WITNESS: So that's what
4 I'm saying. They're relying on my
5 input to make a decision on what will
6 go in the materials.

7 QUESTIONS BY MS. BRANSCOME:

8 Q. Do you have decision-making
9 authority within that company or, as you
10 described it, are you providing advice and
11 input?

12 A. I'm providing advice, but the
13 things I'm advising on are the things that
14 happened. So in other words, they don't have
15 anybody in the company that understands the
16 process of what they can say. So I -- I
17 advise them that you need to remove this
18 language or that this is more appropriate
19 language. They make those changes, and then
20 that is what is done.

21 So I agree, I'm not an employee
22 of that company. I am a consultant working
23 with the company, but it is a little
24 different than some of the work that I do
25 where I -- what I -- the advice that I'm

1 giving is actually something that I know
2 actually happened. Sometimes you give advice
3 to companies, but it doesn't -- we have no
4 idea whether the company actually follows our
5 advice.

6 Q. My question is slightly
7 different, Dr. Plunkett.

8 If you were to give advice to
9 the company that you've referenced as having
10 experience with cosmetic regulation
11 compliance that that company chose not to
12 follow, that company has the ability to
13 ignore your advice, correct?

14 A. Yes, I would imagine that they
15 could do that.

16 Q. Okay. Have you ever drafted
17 regulations that relate to cosmetics?

18 A. Actually drafted a regulation?
19 No, I have not.

20 Q. All right. You reference in
21 your report language out of 21 CFR 740.1, and
22 specifically -- you reference it in a few
23 places. And I can direct you specifically to
24 paragraph 22 in Exhibit 4.

25 A. Yes. I'm there.

1 Q. All right. And do you see here
2 you have replicated language from 21 CFR
3 740.1 that reads, "The label of a cosmetic
4 product shall bear a warning statement
5 whenever necessary or appropriate to prevent
6 a health hazard that may be associated with
7 the product"?

8 Do you see that?

9 A. Yes.

10 Q. And you added emphasis on
11 particular portions of this sentence,
12 correct?

13 A. Yes, I did that, exactly.

14 Q. All right. Now there's a
15 clause in this sentence that states,
16 "Whenever necessary or appropriate."

17 Do you see that?

18 A. Yes.

19 Q. You did not emphasize that
20 language; is that correct?

21 A. That's correct, I did not.

22 Q. What is your understanding
23 as -- what you describe as an FDA regulatory
24 specialist of the meaning of "whenever
25 necessary or appropriate" in 21 CFR 740.1?

1 A. So it's -- first off, you would
2 use the common English language definition.
3 I don't believe that those -- I haven't seen
4 a definition separate within the regulations.
5 Sometimes there will be.

6 So based on that and my
7 experience and the looking into what others
8 have described about this, this is the idea
9 of considering how the product is used, is
10 one of the -- one of the concerns that you
11 have, and whether or not the -- based on how
12 the product is used and how the product is
13 being sold, that in order to prevent a health
14 hazard, a warning hazard -- a warning
15 statement would be needed.

16 Q. Can you cite to me any language
17 within the regulation or even supporting
18 documentation, a comment, something of that
19 nature, that would define "whenever necessary
20 or appropriate" with respect to how the
21 product is used?

22 MS. PARFITT: Objection.

23 THE WITNESS: I don't think I
24 understand your question.

25 Are you asking me to cite to a

1 reference or a part of the regulation
2 where they explain it, or what are you
3 asking me? Guidance document or --

4 QUESTIONS BY MS. BRANSCOME:

5 Q. Yes. Can you point me to
6 anything other than your personal view of the
7 interpretation of this language that would
8 tie the requirement "whenever necessary or
9 appropriate" to how a product is used?

10 MS. PARFITT: Objection. Form.

11 THE WITNESS: I'll have to go
12 look for you whether there's a
13 guidance that states it that way.
14 This is based on my experience in
15 dealing with the products in the past.

16 I think that's also consistent
17 with what is described, I would say to
18 you, within -- it's consistent -- what
19 I'm describing to you, it's consistent
20 as well with how the CIR standard for
21 safety assessment is done, looking at
22 the issue of the -- of the -- of the
23 use.

24 QUESTIONS BY MS. BRANSCOME:

25 Q. When you say that you're basing

1 your interpretation of the clause "whenever
2 necessary or appropriate" on your personal
3 experience, can you point me to something
4 specific?

5 MS. PARFITT: Objection.

6 THE WITNESS: Are you asking
7 me -- are you asking me if I've ever
8 had a company that I worked for that
9 that particular clause in here was
10 extremely important to how we
11 interpreted it? I don't think I can
12 point you to that. I don't recall
13 ever having to do that specifically.

14 Or is it something different
15 you're asking me?

16 QUESTIONS BY MS. BRANSCOME:

17 Q. Dr. Plunkett, I asked you what
18 your basis was for interpreting the language
19 "whenever necessary or appropriate" means
20 that it's related to how a product is being
21 used, and the answer that you provided was
22 that it was based off of your personal
23 experience.

24 So I'm asking you, what is that
25 personal experience that gives you the basis

1 for that specific interpretation?

2 MR. MEADOWS: Objection.

3 MS. PARFITT: Objection.

4 THE WITNESS: So it's in my
5 experience in dealing with companies
6 that make products and what types of
7 warnings are put or not put onto -- or
8 not -- or on labeling. So I don't
9 know how else to answer it other than
10 that.

11 I can go back and look at the
12 guidance documents to see if that is
13 described in another way, but I don't
14 recall that.

15 QUESTIONS BY MS. BRANSCOME:

16 Q. So as you sit here today,
17 you're not able to provide me either with a
18 third-party document or an independent
19 document interpreting "whenever necessary or
20 appropriate" as you've suggested today, nor
21 can you give me specific example from your
22 personal experience; is that correct?

23 MS. PARFITT: Objection.

24 THE WITNESS: Well, I
25 certainly -- I'd have to go back and

1 look at my documents in order -- the
2 first part of your question, I'd have
3 to go back and look. Off the top of
4 my head, I can't tell what I would
5 point you to.

6 On the second one, I think I
7 was telling you, is I don't -- I've
8 never -- I don't have a client that
9 I've worked for where that part of the
10 language was the only issue that I had
11 to deal with when I'm looking at
12 whether or not the product needs a
13 warning or not.

14 So typically -- I'm just
15 telling you that when I have looked at
16 labeling for products and looked at
17 the issue of does it need a warning
18 statement, when I'm reading it as
19 "whenever necessary or appropriate,"
20 I'm looking at whether or not the
21 ingredient that I'm concerned about
22 within the product, how that is used
23 or what the exposure pattern would be,
24 route of exposure, how those things
25 might relate to how I would assess the

1 safety issue at hand. And so that's
2 what I'm trying to tell you.

3 QUESTIONS BY MS. BRANSCOME:

4 Q. Okay. You also have --
5 changing topics a little bit, in this -- in
6 your report marked as Exhibit 4, if you could
7 turn to paragraph 10.

8 On page 7, you state on the
9 first paragraph on page 7, "In other
10 instances I have directed others to perform
11 searches on my behalf," and this is with
12 respect to identifying documents for review
13 in forming your opinions.

14 What did you mean by that?

15 A. So in addition to doing my own
16 searches of the database, sometimes I -- I
17 have called the attorney's office and asked
18 them to -- to do a search for certain things
19 that I'm looking for to add to. So in other
20 words, I have a document I've identified.
21 I'm looking for other documents like that in
22 the large millions and millions of documents
23 that are available. And so sometimes I will
24 ask attorneys to do -- to look in the
25 database for other documents like the ones

1 that I've identified.

2 Q. And without getting into
3 anything that would be -- that would call for
4 information protected by the attorney/client
5 privilege or attorney work product, what
6 percentage of the overall searches for
7 relevant documents from these particular
8 databases that are discussed in paragraph 10
9 would you say that you have done yourself as
10 opposed to directed others to do?

11 A. Well, initially when I first
12 started searching, those were my own searches
13 exclusively. I would say that more recently,
14 in the last year, since I haven't added any
15 real new areas but there's new documents that
16 have become available, so anything -- any of
17 the searches probably in the last year that
18 dealt with new discovery that was produced, I
19 would have asked the attorneys to do some of
20 the searching in that for me. Like I'm
21 looking for documents that are similar to
22 this document that I cited in my original
23 report around this same frame that may be
24 discussing this same topic area.

25 So in the last year I have

1 asked them to do that more than I have done
2 it, but initially it was what I did
3 initially.

4 Q. Okay. Do you keep any records
5 of the various document searches either that
6 you have performed or you have asked to be
7 performed?

8 A. No, I don't. My record would
9 be -- the initial -- the record would have
10 been what I listed in my reliance list for
11 you in the initial report, but since then it
12 would just be what is going to be changing
13 within my reliance list, looking at
14 additional documents. That's the only way I
15 could identify for you. That would be my --
16 my trail to know what was new and what was
17 not.

18 Q. My question is slightly
19 different. Understanding that you have
20 provided to some extent a record of the
21 documents, my question is: Do you have any
22 type of record for the nature of the
23 searches, what it was that you set out to
24 identify in the database and how did you go
25 about finding those documents?

1 A. So that might cross over into
2 work product because it's not my database,
3 but I don't know how to answer that. I mean,
4 I'm sure -- it's very possible that in the
5 database you can track that, but I -- I don't
6 know.

7 MR. MEADOWS: Okay.

8 THE WITNESS: I don't have
9 anything saved on my computer that
10 way, but when you go to the database
11 itself, it's possible you could track
12 that. I just don't have a record on
13 my computer in my office.

14 QUESTIONS BY MS. BRANSCOME:

15 Q. When you made the decision at
16 some point in time -- it may have been even
17 prior to you issuing your first report --
18 that you wanted to look at company documents,
19 did you set out specific categories of
20 documents that you wanted to review?

21 A. Not so much categories but key
22 words. So -- and areas. I guess areas is
23 what I -- yes, I was focusing, for example,
24 in my initial report on documents that
25 described what was known -- what the company

1 was discussing about cancer, ovarian cancer,
2 cancer generally. So that was a key word
3 used.

4 And then I also was linking
5 that in different searches with different
6 time periods such as the NTP review process
7 and dates. You can, you know, narrow down by
8 dates or by the CIR process. Those kinds of
9 things.

10 So I did start with that,
11 trying to understand what -- what is -- what
12 was in the company files or in the files I
13 had access to, the database, that dealt with
14 those kinds of things because those aren't
15 things that I could get to publicly.
16 Obviously in the literature. So I had to --
17 if I wanted to understand what the company
18 knew, I had to go into their database to find
19 out, you know, what they knew -- what they
20 knew or were discussing over time about the
21 ovarian cancer issue or about asbestos in
22 talc or about CIR process, things like that.

23 Q. Using the reports that you have
24 produced, Exhibits 2, 3 and 4, really, and
25 the full -- the entirety of the materials

1 that you have produced in the MDL, is there
2 any way that someone reviewing those
3 documents, and those documents alone, could
4 replicate the searches that you have
5 conducted in the company databases?

6 MR. MEADOWS: Objection.

7 THE WITNESS: I don't know.

8 That's a good question. I've never
9 thought about whether you could
10 replicate or not.

11 I mean, I think I've told you
12 what I did. My strategy was to focus
13 on topic areas. So I think you
14 might -- by topic areas, if you use
15 the same kinds of topics areas as
16 described, I think you would come up
17 with documents that -- what it focused
18 down to.

19 For example, I also would
20 sometimes, as linking those words, I
21 might put in J&J documents only or
22 Imerys documents only, because the
23 database has a variety -- and the
24 PCPC. There's some different ways by
25 the Bates numbers that you can

1 segregate documents as well. But I
2 don't know other than that. That's
3 all I can tell you.

4 QUESTIONS BY MS. BRANSCOME:

5 Q. You would agree with me that
6 your report does not contain a complete
7 explanation of the process by which you
8 identify company documents to review,
9 correct?

10 A. I haven't laid out my search
11 structure, that is true.

12 Q. All right. Now, the articles
13 that you have listed on your reliance list,
14 have you read each and every one of those
15 articles?

16 A. Unfortunately, yes, over time I
17 have. Some of them I have only read parts of
18 them. For example, if I started reading a
19 document and I felt that it was something I
20 pulled that really wasn't directly on point
21 for an area I'm covering, I may not have read
22 every word, but certainly I have been through
23 each of those, yes.

24 Q. Are there any articles in your
25 reliance list, that you maintained on your

1 reliance list, that you read, but then once
2 you started reading decided weren't relevant
3 to the opinions that you were offering?

4 A. I would have to look to answer
5 that for you. I don't know. If you want me
6 to do that, I'd have to look.

7 Q. I ask you more as a process
8 matter.

9 A. Oh.

10 Q. If you pull an article and you
11 start reading it and you realize that it is
12 not relevant to the opinions that you offered
13 in this case, the example that you just gave,
14 is it something that you would include in
15 your reliance list?

16 A. Yes, I -- I have given you
17 everything I retrieved. So if I retrieved
18 it, you would have, yes, absolutely.

19 Q. Okay. So it's fair to say of
20 the articles that are on your reliance list,
21 you could not say as you sit here today that
22 you have read each and every word of each and
23 every one of them, correct?

24 A. That's correct. And I could
25 probably tell you -- I could give you a

1 little guidance in that possibly if I went to
2 my list, I could try to pull some out that I
3 recognize, but that's all I would be able to
4 do for you.

5 Q. Okay. How did you go about
6 identifying what articles you wanted to
7 review in forming your opinions in the MDL?

8 A. So first off, I went back to
9 what I already had. So my MDL report is a --
10 is a compilation of a lot of material that's
11 in my first few reports. That was the basis
12 for some of the things that went into it.

13 So I didn't -- I did do,
14 though, a updating on literature searches for
15 the MDL report, looking for anything new, for
16 example, in the area, especially the area of
17 cancer data or reports of dealing with
18 ovarian cancer either -- or any articles
19 dealing with the link between inflammation
20 and cancer, ovarian cancer, generally.
21 That's one of the areas I updated looking at.

22 And then I did -- I don't think
23 I did any large, new searches, however,
24 because honestly the areas covered here are a
25 little narrower than what was covered here.

1 I don't believe that there was any from the
2 published -- the publicly available medical
3 literature. There wasn't a need to do a
4 whole new area of search. It was more
5 updating the things that I've done in the
6 past.

7 So it's a real easy search to
8 update because you can just put in talc and
9 cancer and just look at -- get lots, but you
10 can then just start chronologically and look
11 what was published in the last year, for
12 example.

13 Q. Okay. Earlier when we were
14 discussing the fact that you in some
15 instances have asked your husband to pull
16 articles, have you maintained any records of
17 the searches that you have done with respect
18 to scientific literature, including the
19 searches that you have asked your husband to
20 do?

21 A. I have not. It's possible that
22 there are records on billing from the library
23 that tells you how many I ordered at
24 different times, but that is the only
25 records, because we do have to pay the

1 library for the retrieval.

2 Q. Okay. And if I understood what
3 you said earlier correctly, you indicated
4 that any article you have ever pulled for
5 review, you have listed on your reliance
6 list; is that correct?

7 A. Yes. And when I -- and let's
8 just make sure we're talking about the same
9 thing.

10 So, you know, in my reports I
11 typically have articles cited in the report
12 separate from the reliance list. So I'm
13 talking about the reliance list, right?
14 Okay.

15 So -- because I do -- I do
16 usually -- I don't know whether I did that in
17 this report, but I typically have a list of
18 articles cited at the back called references,
19 that is, things that you're actually seeing
20 in the report body, and then there should be
21 a separate reliance list sent to you as an
22 appendix. I don't know what the appendix
23 was.

24 Q. Well, so then let's clarify
25 that. So, Dr. Plunkett, when you're

1 referring to the reliance list, are you
2 referring to the list of articles that begins
3 on page 40 of Exhibit 4, or is there a
4 separate document?

5 A. There's a separate document.
6 So it -- that's -- I usually call reliance
7 list the separate document. I call this
8 references cited. So I apologize for that
9 confusion.

10 So these, I have read every
11 word. If it's in my reference list, those
12 are not an issue of not having read every
13 word, and these should all be cited somewhere
14 in the report.

15 Q. Okay. If you could turn to
16 paragraph 21 in your initial report.

17 A. Yes, I'm there.

18 Q. Okay. So we're looking at
19 paragraph 21 in Exhibit 2. This is on
20 page 10.

21 Do you see there is a sentence
22 here that refers to -- it's referring
23 generally to the topic of the ability of talc
24 to migrate from the site of application to
25 the ovaries.

1 Do you see that?

2 A. Yes.

3 Q. And then the next sentence
4 states, "This issue was discussed by
5 scientific and regulatory bodies that review
6 the toxicokinetics of talc."

7 Do you see that?

8 A. Yes.

9 Q. And in parentheses it
10 identified EPA 1992, IARC 2010, and CIR 2013.

11 Do you see that?

12 A. Yes.

13 Q. Okay. And then if you could
14 turn to Exhibit 4, which is your MDL report,
15 at paragraph 43. It's on page 28.

16 Are you with me?

17 A. Yes, I am.

18 Q. You see that the exact same
19 sentence appears -- well, not the exact same.
20 It's been slightly modified to combine the
21 first two sentences. But here you cite only
22 to EPA 1992 and IARC 2010.

23 Why did you remove CIR 2013?

24 A. Because of my further
25 evaluation since my initial report in 2016 of

1 the process that was involved in the drafting
2 of the CIR and the actual production of the
3 report.

4 Q. Is it your position that the
5 migration of talc was not evaluated as part
6 of CIR 2013?

7 A. No. That's not my position,
8 no.

9 Q. Okay. And so would the
10 sentence that's contained in paragraph 43 in
11 Exhibit 4, which is your MDL report, if you
12 cited to CIR 2013 in the parenthetical there,
13 would that not be an accurate citation?

14 A. I believe it would not be an
15 accurate citation because I have formed
16 opinions about the reliability of that
17 document at this point in time.

18 So it has to do with -- I'm
19 citing to authorities here that I believe are
20 reliable as far as the discussion that I see,
21 and it's a different -- I have a different
22 opinion now about the CIR report, which I lay
23 out in pretty detail, I think.

24 In fact, if you go to my
25 section following this now in -- you'll

1 understand one of the issues I had was the --
2 the difference in the evidence that was
3 actually available once you dig into it a
4 little further versus what they actually
5 reviewed. That's one of the issues.

6 Q. And I'll follow up with some
7 more questions about the CIR, but my question
8 here is, the sentence in your report simply
9 states, "The migration of talc internally
10 after perineal application was discussed by
11 scientific and regulatory bodies that review
12 the toxicokinetics of talc."

13 Would it be inaccurate to say
14 that as part of the CIR 2013 process that
15 body did, in fact, discuss the migration of
16 talc internally after perineal application?

17 A. It is true that they did
18 discuss it. I just have an issue with the
19 reliability of their findings.

20 Q. And so you made the decision to
21 just remove it from the citation; is that
22 correct?

23 A. Yes, at this point -- at this
24 point, at this report, that's exactly right.

25 Q. All right. And then I had

1 another question. In paragraph 43, you added
2 two studies from your prior -- that were --
3 that did not appear in your prior report, and
4 it was Gardner 1981 and Edelstam 1997. This
5 related to animal studies showing that in
6 some species talc can migrate from the lower
7 to the upper genital tract?

8 A. Yes.

9 Q. Okay. Were those studies that
10 you were aware of before drafting your prior
11 reports?

12 A. I don't know that they -- I
13 can't answer that without looking at my
14 reliance materials for the original report.
15 I did identify additional articles, and
16 there's also additional articles cited here
17 in earlier paragraph 43 that were not cited
18 in my original report as well. I don't think
19 I had the -- the Kunz article then cited.
20 I'd have to go back and look.

21 So it's possible that they were
22 in my -- when I say my reliance materials, my
23 original report also had a larger list of
24 literature I didn't cite. So I'd have to
25 look. I can't tell you whether I had them or

1 I did not.

2 Q. Okay. With respect to Edelstam
3 1997 study, do you happen to know the title
4 of that article? Even an approximation would
5 work.

6 A. It'll be -- should be back
7 here. Just a second. If it's not here,
8 that's a mistake.

9 Oh, here it is. "Retrograde
10 migration of starch in the genital tract of
11 rabbits."

12 Q. So you are citing that article
13 for the proposition that animal studies have
14 demonstrated that talc can migrate from the
15 lower to upper genital tract?

16 A. Yes, I'm citing it because it's
17 relevant to the issue of particle migration,
18 which talc is a particle. So, yes, that's
19 correct.

20 Q. Okay. But that study did not
21 specifically deal with talc migration,
22 correct?

23 A. No. Well, it -- it's relevant
24 to talc migration, but you're exactly right,
25 they looked at the starch migration, yes. Or

1 particles that were starch, yes.

2 Q. We'll cover this in more
3 detail, but is it your opinion that all
4 particles have similar characteristics with
5 respect to their ability to migrate in the
6 genital tract?

7 A. It's my -- I don't know if I'd
8 state it quite that way. What I would say is
9 that the evidence shows that particles
10 generally have the ability to move up the
11 reproductive tract in women, yes, and that if
12 a particle is one that is similar to talc or
13 some of the other ones where the information
14 has been collected, I would characterize that
15 as being within that, quote/unquote,
16 relevance of particles.

17 That doesn't mean all
18 particles, but certainly in the ones that I
19 have looked at and the data I've relied upon,
20 there's a variety of different types of
21 particles or substances that have been
22 studied and shown to be able to migrate.

23 Q. So let's take Edelstam 1997 as
24 an example.

25 Did you do any analysis that

1 you can point me to that establishes that
2 starch would have a similar migration pattern
3 as talc?

4 A. So I would say that the paper
5 itself shows -- talks about the movement of
6 starch, but are you asking something
7 different?

8 Are you asking me have I done a
9 specific analysis of any differences that may
10 occur between the migration pattern of starch
11 and talc? Is that what you're asking me?

12 Q. That is what I'm asking you.

13 A. I certainly didn't do an
14 in-depth analysis of the differences, no, but
15 based upon my review of the literature, I
16 believe that that paper is relevant to the
17 overall question of migration of particulate
18 through the reproductive tract, including
19 particles of talc.

20 Q. Regardless of whether or not it
21 was an in-depth analysis, can you point me to
22 anything other than just your belief after
23 having read these articles that starch and
24 talc would have similar migratory
25 characteristics in the human or animal

1 genital tract?

2 MS. PARFITT: Objection.

3 THE WITNESS: Again, I haven't
4 done an in-depth analysis. I mean, as
5 a toxicologist, there are differences
6 between starch and talc, absolutely.
7 For example, starch would -- I would
8 expect to be more easily solubilized
9 within fluids, and so that could
10 affect the ability of them to actually
11 not migrate as well as a talc
12 particle, which would be less soluble
13 than the starch would be.

14 And there's -- I even --
15 there's a paper I have in here, and I
16 can look for it if you want, that
17 talks about that difference, and it's
18 one of the issues of cornstarch versus
19 talc, on whether or not you would
20 expect to get the long-term chronic
21 responses with the difference between
22 those two substances.

23 So I do think there's
24 difference, absolutely, as
25 toxicologists generally. And the only

1 reason I'm citing this paper is
2 because I'm trying to be complete
3 about people that have looked at this
4 issue. And certainly it was a study
5 that looked at this issue and talks
6 about the movement.

7 But I wouldn't expect starch
8 and the talc to have the same
9 liabilities, and I also wouldn't
10 expect them to move exactly the same
11 speed maybe. That's very true.

12 QUESTIONS BY MS. BRANSCOME:

13 Q. So you would agree with me that
14 Edelstam is not a study demonstrating that
15 talc can migrate from the lower to upper
16 genital tract, correct?

17 MS. PARFITT: Objection. Form.

18 THE WITNESS: I wouldn't say it
19 that way. What I would say instead is
20 that Edelstam is a study that forms
21 the overall weight of the evidence for
22 the ethics -- for the studies that are
23 available that address the issue of
24 migration, but certainly it is not
25 studying talc. So I don't disagree

1 with you there.

2 Unfortunately, the majority of
3 the information that I have relied
4 upon, and others such as the FDA in
5 making their statements about
6 migration, is not all directed studies
7 just to talc. It's looking at the
8 issue of particle movement.

9 QUESTIONS BY MS. BRANSCOME:

10 Q. Now, in terms of doing your
11 risk assessment -- well, let me get back. We
12 covered this earlier, and I want to return to
13 it for a moment. Just to confirm: For your
14 work in the MDL, you did not do a Bradford
15 Hill analysis, correct?

16 A. I did not sit down and do a
17 Bradford Hill analysis when I started writing
18 this report. I have done a Bradford Hill
19 analysis in the past, which is in my original
20 reports, but I certainly did not redo a
21 Bradford Hill when I sat down to draft my MDL
22 report, that is true.

23 Q. Okay. Let me be more precise.
24 In the report that you have
25 produced that contains a description of your

1 opinions in the MDL, you have not set forth a
2 Bradford Hill analysis in that document which
3 is identified as Exhibit 4, correct?

4 A. That is true, yes.

5 MS. PARFITT: Objection.

6 QUESTIONS BY MS. BRANSCOME:

7 Q. And in fact, the paragraph that
8 you -- or paragraphs that you have in your
9 prior reports that reference a Bradford Hill
10 analysis, those have not -- those have
11 actually not been replicated in any form in
12 Exhibit 4, correct?

13 A. Yes, because, again, it was not
14 my role to do general cause.

15 Q. Okay. So then when we look at
16 the methodology that you employed in reaching
17 your opinions that are contained here in
18 Exhibit 4, how would you characterize the
19 methodology?

20 A. As I have in the report. I
21 talk about it being a risk assessment or a
22 safety assessment, that you could use those
23 terms interchangeably here. And then I've
24 also used a weight of the evidence as a tool
25 to go through the different steps of the risk

1 assessment.

2 Q. Okay. What publication would
3 you direct me to that has used the same
4 methodology that you have used to reach your
5 opinions in Exhibit 4?

6 A. I think I cite you to -- cite
7 you to some of those. You could -- well, the
8 directly relevant one would be looking at the
9 chapter on risk -- toxicology in the
10 reference manual on scientific evidence.

11 You can also go to the NRC
12 report where they -- it lays out the
13 different steps that you use when you kind of
14 break data apart into exposure versus
15 response information.

16 And then I cite to -- there are
17 some guidance documents that I cite to, and
18 this is in paragraph 13. And I'd have to
19 pull them out again to tell you which ones
20 relate to different pieces because some of
21 these are -- some of these documents are
22 specific to only, for example, maybe one part
23 of what I did.

24 But certainly the risk
25 assessment process at IARC is -- they do what

1 I call a hazard assessment. They identify
2 hazard and they couldn't quantify risk, but
3 the steps they go through are essentially the
4 same types of steps that I went through as
5 far as gathering data on not just response
6 but also the potential for exposure and how
7 that relates to the response.

8 And then also the data that
9 I've collected on the biologic effects of
10 talc, toxicology of talc, are also discussed
11 within that document as well.

12 Q. Okay. Focusing specifically on
13 the weight of the evidence tool, as you
14 describe it, is there a particular document
15 or publication that I would go to that could
16 lay out the same process that you used for
17 how you weighted certain pieces of evidence?

18 A. So the documents that I've
19 cited for you in paragraph 13 talk about what
20 weight of the evidence is generally, but if
21 you read what it is, it's essentially a
22 process that each scientist brings their
23 experience, training and judgment to.

24 So I try to lay out for you in
25 my discussion of the literature my thought

1 process as I review each piece of
2 information, and that is what you do as part
3 of weight of the evidence. You gather all of
4 the relevant information that you can find
5 that address the question you're trying to
6 answer, and since I'm looking at both
7 exposure and response, I gather different
8 pools of information.

9 Q. You would agree that there are
10 ways to do a weight of the evidence
11 assessment of published literature that
12 assign, for example, quantitative values to
13 particular pieces of evidence, correct?

14 A. Certain individuals have put
15 together, but there's no one general accepted
16 process that everyone uses. So I -- that's
17 the issue. Again, there are certain --
18 certain cases where I've seen that done, and
19 then there are many -- most cases that it's
20 not what's done.

21 Q. Okay.

22 A. Another body, by the way, that
23 I -- it's new. It's not in paragraph 13. I
24 just want to make sure I tell you that so
25 we're clear. If you look at the Canadian

1 document, they also -- in fact, a lot of what
2 they have, you'll see the same literature
3 described within my assessment as well.

4 Q. So using the Canadian
5 assessment as an example, for instance, in
6 that assessment there were actually values
7 assigned to particular pieces of literature,
8 correct?

9 A. Mainly the epidemiological
10 literature, that is true. Again, but I'm not
11 doing causation, so I didn't approach it that
12 way.

13 But certainly if you look at
14 what I did, it's consistent with that because
15 I talk about the differences between the
16 limitations of a case-control versus a
17 prospective study. I talk about both the
18 positives and the negatives within the
19 database, but I don't lay it out in a table
20 like they do. But it's certainly the same
21 basic process.

22 I was actually quite surprised
23 at how similar the database of information
24 that they reviewed was to what I honed in on
25 as well.

1 Q. Okay. As you were forming your
2 opinions, Dr. Plunkett, about whether or not
3 there is a risk associated with the use of
4 Johnson's baby powder with respect to ovarian
5 cancer, how do you keep track of the pieces
6 of scientific evidence that you have reviewed
7 and the respective weight that you give to
8 them?

9 Presumably you did not read
10 everything in one day, for example?

11 A. No. That's correct. So I
12 typically will -- I typically will save the
13 papers -- when I read the papers, I will
14 often highlight in yellow information that I
15 think is going to -- will be extremely
16 relevant. I don't put notes on the document.
17 I highlight in yellow on the PDF file to use
18 that to write.

19 And I also start drafting
20 report very early, which then gets
21 overwritten and actually ends up looking like
22 an outline that eventually becomes the
23 report.

24 So one of the ways I keep track
25 of things is I may put a paragraph name that

1 I know I'm going to write, such as exposure
2 migration, and then I -- as I'm reading a
3 paper, I'll type in a paper -- the ones that
4 I believe are important to my overall
5 assessment. So I will do that as I'm -- as
6 I'm going through the evidence.

7 So that's one of the tools I
8 use, but I don't keep notes. I just kind of
9 use that as a living document that eventually
10 becomes a report.

11 Q. Do your opinions ever change as
12 you read additional pieces of scientific
13 evidence?

14 A. Yes, it does. It may change.
15 And it often -- often the changes, though,
16 are not that I believe -- with the exception
17 of epidemiology. In other areas.
18 Epidemiology is a little bit different issue
19 when you're reviewing studies.

20 But on toxicology I always
21 start with reviews and regulatory
22 authorities, looking at what others have said
23 generally about the toxicology. And so even
24 though I may refine opinions differently or I
25 might change, I certainly wouldn't agree to

1 work on a project to start with if my initial
2 reviews on hazard, for example, didn't
3 convince me that I believe that there is a
4 hazard. But you refine it from there.
5 That's exactly right.

6 So there are cases, however,
7 where I'm asked to work on a project where
8 there is no review or regulatory authority or
9 any kind of assessment over a period of
10 years, and in those cases there are times
11 when I start working on a project and I stop
12 and say, "I can't do this." Because that
13 happens, yes.

14 So opinions do change sometimes
15 based on review of additional information.

16 Q. Is there any documentation that
17 you've produced either in your report or
18 otherwise in the MDL that would allow someone
19 reviewing the material to understand the
20 order in which you reviewed materials or the
21 specific weight that you assign them?

22 A. So order of review, no. I
23 don't think you would know that other than --
24 you will note order of review if you look at
25 the differences in the literature cited in my

1 original report versus in the MDL.

2 So in my original reliance
3 list, if there were documents that weren't
4 there and they're now here, obviously that
5 tells you it was a review.

6 On the issue of a -- of the
7 weight of the evidence process, the only
8 answer I can give you for that is that
9 articles that I believe are -- are reliable,
10 are relevant and are -- those are kind of
11 the -- you look at the reliability of the
12 studies, whether they're peer-reviewed or not
13 or if they have proper controls put into
14 place, things like that, whether or not
15 the -- they're relevant to the question at
16 hand. That you can get from looking at how I
17 discuss them in the document. But certainly
18 there's no, like, summary of that.

19 But certainly -- I think you
20 understand -- you should understand when you
21 read my report what weight I'm giving based
22 on how I'm describing those -- those
23 materials. I mean, it's --

24 Q. Well, for example, you do have
25 different studies that you've identified in

1 your report that have been criticized by
2 others at some point in time, correct?

3 A. Yes, that's true.

4 Q. Okay. Now, in some instances
5 you state that you then give little weight to
6 those studies, correct?

7 A. Yes.

8 Q. But in other instances you find
9 the criticized study to be helpful and
10 informative, correct?

11 A. That's true. Because, again,
12 judgment -- as anybody does weight of the
13 evidence, different scientists can have
14 different judgment.

15 Mainly, I think, when I look at
16 the differences in that -- in that regard, I
17 think you should pay attention to what the
18 person is. So as a toxicologist, I may view
19 a certain type of -- piece of data very
20 differently than an epidemiologist may view
21 it, as far as the reliability or the
22 relevance, because we're coming at it from a
23 different training and experience and
24 judgment -- set of judgment on what is
25 important to a toxicologist when I'm talking

1 about risk versus how an epidemiologist might
2 talk about risk.

3 Q. Could two different
4 toxicologists review the same piece of
5 literature and give it very different weight?

6 A. I don't know about different
7 weight, but they certainly -- I know people
8 come to different conclusions based on their
9 overall assessments. That happens,
10 definitely. I mean, there are always going
11 to be individuals that look at things
12 differently.

13 I know in this case there are
14 people -- I've seen defense experts that
15 reports in -- not in the MDL but in other
16 cases, where people disagree with some of my
17 opinions, and I disagree with their opinions.
18 That happens.

19 Q. Okay. And so if I were --
20 well, let me just ask something. You have
21 not provided any sort of quantitative
22 assessment of the weight that you gave
23 different pieces of evidence that you cite in
24 forming your opinions in the MDL, correct?

25 MS. PARFITT: Objection.

1 Misstates her testimony.

2 MR. MEADOWS: Objection.

3 THE WITNESS: So I don't report
4 for you a table where I quantify that,
5 that is correct, but certainly that
6 is -- because, again, based upon
7 looking at the way that I was trained
8 and the documents that I'm talking --
9 I'm pointing you to to describe how to
10 do weight of the evidence, it is
11 not -- it is not a numerical exercise,
12 how many here, how many there, this
13 one gets 5 points because of this or
14 6 points because of this.

15 It's more an issue, again, of
16 judgment. It's the idea of looking
17 across all of the available
18 information and determining whether or
19 not, based on that, it's your opinion
20 that there -- that, for example,
21 talc -- talc's toxicity profile
22 includes cancer. That's one of the
23 judgments -- weight of the evidence
24 judgments you make, for example.

25

1 QUESTIONS BY MS. BRANSCOME:

2 Q. So -- but, Dr. Plunkett, just
3 to be clear, you do not provide a numerical
4 value to the particular pieces of evidence
5 that you have considered as part of your
6 weight of the evidence assessment in the MDL,
7 correct?

8 MS. PARFITT: Objection. Form.

9 THE WITNESS: So I do not
10 provide a numerical value as you see
11 it laid out, for example, in the
12 Canadian table, but certainly I do
13 judge articles that I include in my
14 weight of the evidence based on a
15 system that includes different
16 considerations such as -- like I said,
17 peer-reviewed or not, that makes an
18 issue.

19 Whether or not the study that's
20 being reported is the only one -- the
21 first or is this something that is --
22 that is describing an assessment
23 that's been done by someone else and
24 so you see a repetition or a
25 consistency among the studies that

1 you're looking at.

2 The robustness of the data.

3 For example, the NTP GLP quality
4 animal study, very high quality in the
5 weight of the evidence. And I talked
6 to you about that. In fact, it --
7 even though people criticize that
8 study, that study is very valuable for
9 looking at biologic changes that are
10 consistent with a carcinogenic
11 mechanism being initiated.

12 So even though you may say that
13 you can't quantify risk from that
14 animal study as far as calculating a
15 cancer potency factor, what you can do
16 is use that study of high quality to
17 make judgments within a weight of the
18 evidence for risk.

19 QUESTIONS BY MS. BRANSCOME:

20 Q. Dr. Plunkett, you understand I
21 have seven hours today, and I -- while I'm
22 very interested in the answers that you give,
23 if we could just -- we will get to things
24 like NTP when we get there, if you could just
25 attempt to answer the question that I've

1 asked.

2 I simply asked the question:
3 Are there numerical values assigned to the
4 particular pieces of evidence that you have
5 considered as part of your weight of the
6 evidence assessment in reaching your opinions
7 in the MDL; yes or no?

8 A. And I said to you, not in the
9 way that it's done -- I assume you're
10 referring to something like what was done --
11 what's in the Canadian epidemiology table. I
12 have not done that, no.

13 Q. Okay.

14 A. That's exactly right.

15 Q. Have you provided a qualitative
16 chart, for example, of the evidence that you
17 have considered in forming your opinions in
18 the MDL?

19 MS. PARFITT: Objection. Form.

20 THE WITNESS: I don't know what
21 you mean by qualitative chart. I
22 certainly have -- I certainly, I
23 believe, have given you qualitative
24 descriptions of my weight within my
25 discussions of each study, yes, I have

1 done that.

2 QUESTIONS BY MS. BRANSCOME:

3 Q. You mention in response to the
4 prior question that you have a system for
5 weighting the pieces of evidence that you
6 have reviewed.

7 Can you point me to paragraphs
8 in your report marked Exhibit 4 that would
9 outline in detail the system that you used to
10 apply different weight analysis to different
11 pieces of evidence?

12 MS. PARFITT: Objection. Form.

13 THE WITNESS: And I think I
14 answered that, that there's no system
15 written down by anyone. But what
16 there is, instead, is if you read
17 these -- if you read these
18 descriptions of use of weight of the
19 evidence that I've cited in
20 paragraph 13 as well as the discussion
21 of methodology in the Canadian
22 document, that is consistent with what
23 I do. It's the idea that you start
24 with a literature search for
25 peer-reviewed, publicly available

1 information. You look at the quality
2 of the studies, the statistically
3 significant findings. Those are all
4 things that are discussed within these
5 documents I'm pointing you to.

6 QUESTIONS BY MS. BRANSCOME:

7 Q. Now, you --

8 A. But it's -- it's -- I don't
9 know of anyone who has written down a
10 specific system that applies in all
11 circumstances, no.

12 Q. Okay. Have you written down a
13 system that applies specifically in this
14 case?

15 A. I think I have tried to do that
16 for you when I describe what I did.

17 Q. Okay. You just referenced the
18 fact that your system can be found in the
19 Canadian document.

20 You agree that the Canadian
21 analysis was actually published or produced
22 after you had completed your report in the
23 MDL, correct?

24 MS. PARFITT: Objection. Form.

25 THE WITNESS: Certainly it was

1 published afterwards, and what I
2 thought I said to you was that if you
3 look at that document -- it's not in
4 paragraph 13, but if you look at that
5 document, it lays out a process. And
6 I wouldn't call it a system. It's a
7 process. It's a process by which you
8 screen information for relevance to
9 the question being asked and how,
10 then, based on that, you look at
11 characteristics of that information
12 such as -- and I tried to give you
13 some of those.

14 And I've said this before in
15 depositions in these cases. You know,
16 you look at the issue of whether or
17 not the study was peer-reviewed,
18 whether or not there was
19 statistically -- statistical
20 significance or at least statistics
21 applied to the data. What was the
22 quality of the study as far as the
23 size in order to be able to answer the
24 question being asked. Those are the
25 kinds of things that you look at.

1 And then also the question --
2 when you're looking at a specific
3 question, you may pull in -- like you
4 asked me about the starch particle.
5 You may pull in things that you give
6 less weight because obviously that's
7 not just talc, that's starch, and you
8 have to consider that. So that is
9 part of the process.

10 QUESTIONS BY MS. BRANSCOME:

11 Q. Dr. Plunkett, the question I
12 asked you simply was: The paper that you
13 reference that contains some detail about the
14 Canadian analysis, that was published after
15 you completed your report that's marked here
16 as Exhibit 4; is that correct?

17 MR. MEADOWS: Objection.

18 THE WITNESS: Yes, and I
19 believe I answered that at the start.
20 I usually try to answer your question,
21 and then I try to explain further some
22 details I think are important context
23 on my answer.

24 QUESTIONS BY MS. BRANSCOME:

25 Q. I understand that,

1 Dr. Plunkett. You have given many
2 depositions. You understand I can ask you
3 for more detail if that would be helpful to
4 me.

5 If you could, just focus on the
6 question that I asked, and we can explore
7 additional areas if that's something I'm
8 interested in doing.

9 Okay?

10 MR. MEADOWS: Objection.

11 She's --

12 MS. BOCKUS: Break?

13 MR. MEADOWS: After I finish my
14 objection.

15 She's going to answer the
16 question as thoroughly as she feels
17 like she needs to answer the question
18 based on the way you ask it.

19 Want to take a break now?

20 MS. BRANSCOME: We can go off
21 the record.

22 VIDEOGRAPHER: We're going off
23 the record at 10:41 a.m.

24 (Off the record at 10:41 a.m.)

25 VIDEOGRAPHER: We are back on

1 the record at 10:56 a.m.

2 QUESTIONS BY MS. BRANSCOME:

3 Q. All right. Dr. Plunkett, we
4 started talking a little bit about the CIR
5 analysis that was done in 2013.

6 Am I correct you no longer
7 consider that reliable? Is that your
8 opinion?

9 A. Yes.

10 Q. Okay. And you identify in your
11 report marked as Exhibit 4, I believe it's
12 paragraph 56?

13 A. Yes, that's correct. And I
14 think I talked about it later on as well, but
15 definitely I do here.

16 Q. Okay. And in paragraph 56, you
17 state that the CIR panel failed to account
18 for all the studies that informed on the
19 issue of migration of particles such as talc
20 upwards through the reproductive tract.

21 Is that your opinion?

22 A. Yes.

23 Q. Okay. And then you state that
24 because of that you assign, quote, little
25 weight to the conclusions reached by the CIR

1 panel; is that correct?

2 A. Yes.

3 Q. And so is it your view that a
4 study or an analysis that reaches a
5 particular conclusion should be assigned
6 little weight if it fails to consider all
7 relevant scientific evidence to the issue
8 that it's evaluating?

9 MS. PARFITT: Objection.

10 THE WITNESS: I think it
11 depends on the situation, but that
12 could be the case, yes. It depends
13 on -- on the -- depends on -- I think
14 it would depend on each case, the
15 question being asked, and what was
16 omitted. But, yes, I think it could.

17 QUESTIONS BY MS. BRANSCOME:

18 Q. Okay. And in this situation
19 you identify -- I believe you claimed that
20 eight human studies were not considered by
21 the CIR 2013 panel; is that correct?

22 A. Let me look at the number, but
23 that sounds about right. Yes.

24 Q. All right. And returning,
25 actually, to your prior answer, you said that

1 the failure to consider all relevant
2 scientific evidence on a topic would lead you
3 to assign little weight to a particular
4 conclusion. You said that that could happen.

5 Under what circumstances would
6 you assign a conclusion little weight for
7 failing to consider what you consider to be
8 all relevant pieces of scientific literature?

9 A. Well, I think it depends --
10 well, the reason I specifically addressed
11 that in this case is because that was -- the
12 conclusions about migration is the main
13 reason why the CIR panel then draws
14 additional conclusions later on.

15 So my issue is, migration was
16 key to what -- the decisions they made about
17 the safety issues of talc. And so in that
18 particular case, this -- this failure to
19 consider all the evidence was extremely
20 important, in my view, and I gave it little
21 weight.

22 There might be a situation
23 where some -- for example, you may only look
24 at six or eight studies, even though there
25 may be dozens out there. You may have a

1 reason for why you only looked at six or
2 eight, or it may be -- and as a result you
3 may lay that out and, therefore, you may
4 still give weight to conclusions drawn. Or
5 it may be that the six or eight are --
6 studies that you discuss are not -- the
7 weight is not affected by what you've
8 omitted.

9 I believe that the weight is
10 affected by what is omitted when you look at
11 some of the articles being review articles,
12 which give you an understanding of what was
13 generally accepted within the scientific
14 community when you get to reviews, those
15 kinds of things. So it really is a
16 case-by-case basis.

17 But certainly I do believe that
18 it is possible that in another circumstance
19 where things are omitted you would come to
20 the same conclusion, that you give those
21 conclusions less weight.

22 Q. Is there a way, if someone were
23 try to replicate the weighting of particular
24 evidence based upon your process, for them to
25 know whether or not the omission of a

1 citation of certain studies means that a
2 study should be given little weight or
3 whether it wouldn't affect the weighting of
4 that scientific article?

5 MS. PARFITT: Objection. Form.

6 THE WITNESS: So I think this
7 is the issue of judgment, training and
8 experiencing that is applied to all
9 such assessments, and this is why
10 different scientists may come to
11 different conclusions. But certainly
12 it is -- it was important to my
13 assessment on this issue because of
14 the prominent role that the CIR report
15 gives to their conclusions here for
16 why they then drew conclusions about
17 safety. And so that link was
18 extremely important.

19 MS. BRANSCOME: Can we pause
20 for just a moment?

21 VIDEOGRAPHER: We are going off
22 the record at 11:00 a.m.

23 (Off the record at 11:00 a.m.)

24 VIDEOGRAPHER: We are back on
25 the record at 11:01 a.m.

1 QUESTIONS BY MS. BRANSCOME:

2 Q. Okay. Of the eight studies
3 that you identify on page 37 of your report
4 that you contend the CIR panel did not
5 account for, do any of those eight studies
6 specifically discuss the migration of talc in
7 human subjects?

8 A. No, I don't believe they do,
9 but there are a couple of these studies that
10 I found to be extremely important if you want
11 me to explain that to you.

12 Q. Do you break out in your report
13 in any other paragraphs which of these eight
14 articles you consider to be extremely
15 important?

16 And if you could just point me
17 to paragraph numbers, that's good enough if
18 you have, in fact, broken them out.

19 A. I have. I -- this whole
20 section I break -- I talk about each one
21 individually. So I think you can tell by
22 what I read -- what I'm discussing what I
23 thought was important and informative about
24 each of those.

25 Q. Do you rank the eight studies

1 in any way by their importance to you?

2 A. Not with any numerical rank,
3 no, but certainly I think I do that for you
4 when I talk about the studies. I give you an
5 understanding of ones that I think are
6 particularly informative and ones that are
7 not.

8 So, for example, I weight the
9 human data -- I think I tell you that -- more
10 than the animal data because of the
11 differences between the reproductive tracts
12 of humans versus animals generally, upright
13 versus -- upright and habits and things that
14 humans do that relate to insertions in and
15 out of the reproductive tract, I guess is a
16 nice way to describe it, versus an animal,
17 that those can have, and then also the
18 differences between animals and humans in
19 terms of bursal sac around the ovary, those
20 kinds of things.

21 So I do -- that -- I guess that
22 ranking I do give you here. I tell you that
23 I think these -- I think that the most
24 relevant are going to be the human studies
25 versus the animal studies.

1 Q. Right.

2 So my question specifically is,
3 where would you point me to in your report to
4 understand the weight that you gave each of
5 these particular eight studies?

6 A. At my descriptions of those
7 studies and what I describe. That's all I
8 can tell you.

9 Q. And I'm just asking,
10 Dr. Plunkett, can you point me in the report
11 to where that discussion takes place?

12 A. It takes place -- I have a
13 discussion for each study, and I would -- and
14 if you read what I say about each study, I
15 try to go through what the strengths and
16 weaknesses of those studies are.

17 And so those -- that would be,
18 let's see -- you want me to give you the
19 starting paragraph?

20 Q. So, for example, Parmley and
21 Woodruff. Can you point me to where in your
22 report you discuss Parmley and Woodruff, such
23 that I can understand the weight that you
24 gave that particular study?

25 A. So the year of it is...

1 So I think I discuss it in
2 paragraph 44, and so I describe for you what
3 important information is in there, which is
4 the information that I take as forming part
5 of my weight of the evidence.

6 So one of the most important
7 things is what -- they have a figure they
8 show, and they're showing -- which is one of
9 the unique figures in all of the published
10 literature. But it talks about the
11 differences between the female reproductive
12 tract and the male reproductive tract, and it
13 shows the actual -- it talks about a
14 discussion of movement from substance in the
15 environment through -- into the vagina, into
16 the fallopian tubes. So it's a paper that
17 addresses that very specific issue.

18 Q. So my question to you, though,
19 is, where do you have a discussion of the
20 weight that you give to these particular
21 articles?

22 A. So the discussion of the weight
23 has to do with the information described. I
24 don't give them a numerical ranking. I told
25 you that.

1 So what I do is, when I'm
2 discussing about these -- all of these papers
3 here contribute to my weight of the evidence.
4 And if it's a human study, I'm giving those
5 more weight than I'm giving animal studies.
6 And that's described.

7 And then within papers I'm
8 pulling out information that contributes to
9 what I think is important about what the
10 study says, and that -- and the importance of
11 what is described within the study
12 contributes to my weight.

13 And I don't know how else to
14 describe it to you. That is the process that
15 scientists go through when they evaluate
16 data.

17 Q. And so my question to you:
18 Earlier you said of these eight studies, some
19 of them were particularly important to you.

20 How would I, using only what's
21 written in your report, understand which of
22 those eight studies was of particular
23 importance to you?

24 A. So it would have to do with
25 what I discuss about the study. So I'm

1 telling you, when I -- if you look through
2 this entire section, this is the Parmley and
3 Woodruff paper. It is important because it
4 addresses the specific issue of movement of
5 environmental substances from the outside to
6 the inside. So I'm giving that importance in
7 my evaluation because of what that author is
8 actually discussing.

9 I don't know how else to
10 describe that. I apologize. I mean, to me,
11 weight of the evidence is a process that
12 scientists use bringing their training and
13 experience and judgment, and it's not a
14 numerical process across the board, it just
15 is not, based on the way weight of the
16 evidence is used within science.

17 Q. Now, Dr. Plunkett, though, you
18 would acknowledge that if you wanted to
19 assign numerical values to the studies, that
20 has been something that has been done by
21 other authors and other authors on whom you
22 rely, correct?

23 MS. PARFITT: Objection. Form.

24 THE WITNESS: I don't believe
25 that's true. I'll need to look -- I

1 don't believe that's true with respect
2 to the biological information. I
3 believe it may be true with respect to
4 the epidemiology studies.

5 You want me to look real quick
6 to confirm that? I can do that really
7 quick, but...

8 QUESTIONS BY MS. BRANSCOME:

9 Q. I'm simply saying, could you
10 assign a numerical value if you chose to do
11 so?

12 MR. MEADOWS: Objection.
13 Objection. Form.

14 THE WITNESS: And I'm -- what
15 I'm trying to say to you is I think
16 that I -- that there is no one set of
17 rules that you would assign in order
18 to do that for all the types of
19 studies that you weigh.

20 I would agree that I have seen
21 it routinely done -- well, not
22 routinely, but I've seen it done
23 within the epidemiological community
24 when they go through the epi data.
25 But not -- it's not something that

1 I've seen done when you talk about
2 weight of the evidence as part of a
3 human health risk assessment. That is
4 not something that scientists
5 typically do as far as giving
6 numerical rankings.

7 QUESTIONS BY MS. BRANSCOME:

8 Q. You're familiar with the
9 National Cancer Institute, correct?

10 A. Yes, I am.

11 Q. All right. They are considered
12 to be the nation's leader in cancer research,
13 correct?

14 MS. PARFITT: Objection to
15 form.

16 THE WITNESS: The National
17 Cancer Institute?

18 Yes, they are. I don't know if
19 they're "the" leading, but they're one
20 of the leading, that's true.

21 QUESTIONS BY MS. BRANSCOME:

22 Q. Okay. And you're familiar with
23 publications that they issue called physician
24 data queries?

25 A. Yes, I am.

1 Q. All right. And you are aware
2 that there is, in fact -- called PDQs,
3 correct?

4 A. That's the abbreviation, yes.

5 Q. Right. And you're aware that
6 the National Cancer Institute has in fact
7 published a PDQ that addresses a potential
8 connection between talc and ovarian cancer,
9 correct?

10 A. I'm aware of several that have
11 been done over the years, but, yes, I'm aware
12 of that.

13 Q. And have you reviewed those?

14 A. Yes, I have.

15 Q. Are they listed on your
16 reliance list?

17 A. No, but they're listed within
18 the materials as discussed within my
19 depositions, and I thought -- and my
20 testimony. I thought that was part of my
21 reliance list. I believe that it -- it was
22 in my reliance list, is encompassing all of
23 the testimony as well as the actual
24 documents. Maybe I'm mistaken, but that was
25 my understanding.

1 Q. Okay. If they are not on your
2 reliance list, should they be?

3 A. I believe that they are on my
4 reliance list by it having been pointed to as
5 part of the testimony that I have given and
6 the documents that I have relied upon during
7 testimony.

8 Q. Okay. And you are aware that
9 they have issued a PDQ that -- on the website
10 as of today, correct?

11 A. I haven't looked today, so I'm
12 sure -- but I know that -- I don't believe it
13 has been removed, so I believe that there is
14 something there, yes.

15 Q. All right. And what is your
16 understanding of the position stated in the
17 PDQ with respect to a possible link between
18 talc and ovarian cancer?

19 A. So I'd have to look at the one
20 today to tell you what it says, but it's
21 evolved over time and it's changed over time,
22 and I have specific opinions that I've
23 expressed at trial about that issue.

24 Do you want me to go into that
25 details or I mean --

1 Q. I'm not asking about your
2 opinions about what their position is. I'm
3 simply asking you, Dr. Plunkett, the most
4 recent NCI PDQ that you have reviewed, what
5 is the position that the National Cancer
6 Institute has taken with respect to the
7 relationship between talc and ovarian cancer?

8 A. So I would want to pull it out
9 to give you the specific statement of their
10 position, but their position has changed such
11 that later in time they've weakened the
12 link -- their statements about the link
13 between ovarian cancer and genital talc use.

14 So it used to be seen as a
15 cause, and now I believe it's not seen as a
16 cause. I don't know the exact language,
17 though. I'd have to look at it as -- maybe
18 risk factor is the better word to use.

19 And I need to look at the most
20 recent one. And that would be the best way.
21 Let's just see what it says.

22 Q. Okay. 'Cause is it your
23 position as you sit here today that the
24 National Cancer Institute has ever issued a
25 statement that talc causes ovarian cancer?

1 A. I believe it was listed as a
2 risk factor for ovarian cancer in the older
3 PDQs.

4 (Plunkett Exhibit 7 marked for
5 identification.)

6 QUESTIONS BY MS. BRANSCOME:

7 Q. I do have a copy here. Just
8 for the sake of the record, we will mark this
9 as Plunkett Deposition Exhibit Number 7.

10 Handing a copy to you,
11 Dr. Plunkett, do you recognize the document
12 that I just handed you that's marked as
13 Exhibit 7?

14 MR. LOCKE: What's the date of
15 that?

16 MS. BRANSCOME: This was
17 printed on December 14, 2018.

18 THE WITNESS: It's -- the
19 updated date is June 22, 2018, if that
20 helps.

21 MR. LOCKE: Yes, thank you.

22 THE WITNESS: I have seen this
23 one, yes.

24 QUESTIONS BY MS. BRANSCOME:

25 Q. All right. And you can review

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1 any -- whatever portion of this is helpful to
2 you.

3 And then if you could answer my
4 question, Dr. Plunkett, of what is the
5 position as stated in Deposition Exhibit
6 Number 7 of the National Cancer Institute
7 with respect to the relationship between talc
8 and ovarian cancer?

9 A. So I would be looking at the
10 section on page 12 of 18, and maybe you're
11 looking somewhere else, but that's where they
12 actually talk about perineal talc exposure.
13 And it's under the section where they have
14 now moved into factors with an adequate
15 evidence of an association and they describe
16 it here. So they're calling it an
17 association where the weight of the evidence
18 is not adequate to support that association.

19 Q. All right. And so the first
20 sentence of the section under perineal talc
21 exposure states, "The weight of the evidence
22 does not support an association between
23 perineal talc exposure and an increased risk
24 of ovarian cancer."

25 Did I read that correctly?

1 A. You did read that correctly.

2 Q. All right. And it indicates
3 that "results from case-control and cohort
4 studies are inconsistent."

5 Did I read that correctly,
6 Dr. Plunkett?

7 A. You did.

8 Q. And the question that I would
9 ask simply is, do you discuss the National
10 Cancer Institute PDQ in the report that
11 you've issued in the MDL, which is identified
12 as Exhibit 4?

13 A. I don't specifically discuss
14 this document, no, I do not.

15 Q. Okay. And you understand that
16 the NCI PDQ did a weight of the evidence
17 analysis that followed a formal evidence
18 ranking system, correct?

19 MS. PARFITT: Objection.

20 THE WITNESS: So I -- it's not
21 laid out here, but they do have a
22 process they use.

23 Is that what you're asking me?

24 QUESTIONS BY MS. BRANSCOME:

25 Q. Yes.

1 A. Yes. And again, they're
2 ranking the epidemiological data, and so I
3 understand that that is there, yes.

4 Q. Now, you've said a few times
5 that you could qualitative -- you could give
6 a quantitative weight to an epidemiological
7 study, somehow suggesting that it is
8 different from other types of studies.

9 What is it about a
10 toxicological study, for example, that would
11 prevent someone from giving a quantitative
12 weight in a weight of the evidence analysis?

13 A. Because it is just what is
14 typically done and not done. There are
15 certain practices within the community, what
16 is kind of -- I would say that scientists use
17 routinely, or scientists have used. Not all
18 scientists give numerical rankings to
19 epidemiological data either, because even
20 within a Bradford Hill assessment, when you
21 use the considerations, there's no
22 requirement for ranking studies in order to
23 meet the requirements of use of that
24 methodology.

25 Q. Okay.

1 A. But I have seen it done in the
2 epidemiology community, and that is the most
3 common place I see it. I do not see other
4 toxicologists that are assessing animal
5 studies and in vitro studies doing it that
6 same way.

7 When you do a human health risk
8 assessment, that isn't routine practice to do
9 numerical rankings on studies.

10 Q. Okay.

11 A. At least in my experience and
12 in my training, and I was trained in the use
13 of risk assessment by one of the individuals
14 who actually invented the process.

15 Q. Okay. Okay. But do you
16 consider the epidemiological evidence as part
17 of your risk assessment in the MDL?

18 A. I do, because I'm looking at it
19 in the context of what is out there and
20 what's available. I don't always have human
21 data when I do risk assessments, but in this
22 one I do. So I do consider them, yes.

23 Q. Okay. Did anything prevent you
24 from doing a quantitative assessment of the
25 weight that you were giving different pieces

1 of epidemiological evidence?

2 A. If by -- you mean prevent, was
3 someone stopping me from doing that, no. But
4 if you ask what would be standard practice
5 based on my experience, I would not be doing
6 that.

7 Q. Has anyone -- and I'm not
8 referring in this case to any attorneys. But
9 has anyone reviewed your -- the weighting
10 that you gave specific pieces of evidence as
11 essentially a form of a peer review process?

12 A. If by that you mean have I
13 submitted my opinions for publication, no, I
14 have not done that. Part of -- that's partly
15 driven by my understanding of the evidence
16 that I reviewed, that some of it may not be
17 something that I should be discussing
18 necessarily in a public form outside of the
19 cases I'm working in.

20 But certainly I have not
21 submitted it for publication, if that's what
22 you mean. No, I have not done that.

23 Q. Okay. Has the methodology that
24 you have used in the MDL, has that been --
25 have you submitted any type of analysis using

1 that methodology for publication even outside
2 of particularly looking at Johnson's baby
3 powder, for example?

4 A. Yes, in -- if you look at my
5 publications that describe risk assessments
6 that I have done. So the one that would come
7 to -- to play that's similar as far as the
8 scope of the weight of the evidence would --
9 at least with the animal and the in vitro
10 studies, would be the paper that I published
11 on copper, looking at the database of copper
12 and identifying points of departure and
13 target organs and risk -- risk issues based
14 on copper use in humans, trying to set a --
15 understand what a safe exposure level could
16 be to copper in water. And that was
17 published -- that actually was one of the
18 papers that's published with Dr. Krewski, who
19 is one of the authors of this risk assessment
20 in Canada.

21 Q. And is it your position that
22 you follow the same methodology in what
23 you've reported in the MDL with respect to
24 Johnson's baby powder that you did in your
25 analysis of copper?

1 A. Yes, with the process of going
2 through all of the publicly available
3 information, putting it together based on its
4 relevancy and reliability.

5 We did a process where we
6 grouped it based on animal versus human, just
7 like I've done here. And we call it the
8 bins, but it's the same idea. I have a bin
9 of human idea, I have a bin of animal data
10 and a bin of in vitro data. And so, yes, the
11 process was very, very similar.

12 Q. Okay. Returning back to some
13 documents that you chose not to cite in your
14 report, you do not discuss the Gonzales 2016
15 study in your report for the MDL, correct?

16 MS. PARFITT: Objection. Form.

17 THE WITNESS: I'll have to
18 look. It is not cited in the
19 reference list to my report, that is
20 true. So that means it would not be
21 mentioned specifically in the body of
22 the report.

23 QUESTIONS BY MS. BRANSCOME:

24 Q. You're familiar with the
25 Gonzalez 2016 study, correct?

1 A. If you want me to talk about
2 it, you'd have to pull it out for me, but I
3 know the name, yes.

4 Q. Okay. And it was looking at an
5 association between the perineal use of talc
6 and ovarian cancer, correct?

7 A. That, I'd have to look at it to
8 tell you. I believe it was a human study
9 that would be consistent with that, but I
10 need to pull it out to look at it.

11 Q. All right. Do you, as you sit
12 here today, do you know why you did not
13 discuss it in your report?

14 A. I wasn't doing a full causation
15 analysis in this report, so as a result I'm
16 not trying to characterize every piece of
17 human data. But I certainly am looking at
18 the consistency across the studies, and
19 that's what I've done.

20 And I mention it here. I do
21 think I mention here that there are studies
22 that came to different conclusions than the
23 ones that I'm specifically describing.

24 Q. Okay. And so why is it that --
25 why is it acceptable for you to choose not to

1 include something like the Gonzales 2016
2 study, but yet you will disagree the
3 2013 -- the CIR 2013, you will give it little
4 weight for not discussing particular studies?

5 A. So that's a very different
6 exercise. You want me to explain my thinking
7 on that? I can do that for you, but I
8 believe that's apples and oranges question.

9 My reasons for giving little
10 weight to the CIR overall assessment versus
11 my weight or the assessment I make of an
12 individual piece of data, that's different.
13 And that's what you're describing for me.

14 And I believe Gonzales is in my
15 overall reliance list, so I have read
16 Gonzales. It is something that I have
17 considered; it's not something that I've
18 cited in my paragraphs. So it doesn't mean
19 it didn't go into my weight of the evidence,
20 because I do have it and I have reviewed it.
21 I just don't recall the details on it.

22 Q. Is it your position as you sit
23 here today that you know for sure that the
24 CIR panel did not -- was not aware of or even
25 considered any of the eight studies that you

1 contend the omission of which makes it of
2 little weight?

3 MS. PARFITT: Objection. Form.

4 THE WITNESS: I would say I'm
5 99.9 percent sure, based on the
6 process that is -- that goes in. And
7 if you want me to explain, I'll tell
8 you why I feel that level of surety.

9 You know, I can always say that
10 maybe there was someone that came to
11 the panel that did a search on their
12 own, but that is not what's done. The
13 individuals that come to the panel are
14 given a body of information provided
15 to them in written form that they
16 review. So it's not like they -- they
17 have access to anything that isn't
18 cited in the actual report.

19 QUESTIONS BY MS. BRANSCOME:

20 Q. Okay. The eight articles that
21 you discuss that are not mentioned in the CIR
22 panel's work, they are publicly available
23 pieces of scientific literature, correct?

24 A. Yes, which was why it's
25 interesting to me that those were not grabbed

1 and included within -- within the assessment
2 done by the -- by the PCPC's group that
3 handles CIR -- handled the CIR process here.

4 Q. Okay. We received just before
5 your deposition, a few days in advance, a
6 list of materials that have been added to
7 your reliance list since you produced your
8 report in this case.

9 Did you provide that list of
10 materials to counsel to -- are you aware of
11 the materials that were identified?

12 A. Yes, I am. They're ones that I
13 have reviewed since my report and -- yes,
14 which would have been, I believed, important
15 for you to know about, because obviously you
16 wouldn't know if I hadn't provided that to
17 you, and fair game for you to ask me about.

18 Q. On that list was contained a
19 number of news articles.

20 A. Uh-huh.

21 Q. Are news articles pieces of
22 scientific information that you typically
23 consider in performing a risk assessment?

24 A. No, they're not part of my risk
25 assessment, but they -- but they were

1 relevant to -- they were relevant to my
2 overall assessment of the issue of what the
3 company is doing with regard to public
4 dissemination of information.

5 So it's not the risk assessment
6 part. It's more on the issue of the -- when
7 I talk about the different influences of the
8 company on public dissemination of
9 information, I went through the different
10 specific issues. So this would be a specific
11 issue related to a news report that someone
12 comes out with, the Reuters report, and then
13 looking at what the company is saying in
14 addition to that.

15 So it's understanding -- for
16 example, the documents that Reuters
17 discusses, many of those I'm sure I have
18 seen, although I don't have access to -- I
19 wasn't able to go on websites and download
20 everything that they cite. But certainly
21 they looked familiar, some of the ones I did
22 see.

23 So it's that issue of -- the
24 last part of my report, I think. Want me to
25 tell you the section? It would be in the

1 section on the role of the industry in
2 Section 7.

3 Q. Okay. So the newspaper
4 articles are not something that you are
5 considering as part of your analysis of
6 whether there is a risk of ovarian cancer
7 from Johnson's baby powder, correct?

8 A. No, that's a separate issue
9 because it's not -- it's not scientific data,
10 per se.

11 Q. Okay. All right. Now, if you
12 could turn to paragraph 31 in your report.

13 Okay. You discuss the
14 biological effects of talc in this paragraph
15 and in others, correct?

16 A. Yes, I would call this my
17 introductory paragraph to transition into a
18 specific topic, yes.

19 Q. Okay. And you talk here about
20 the structure and size of talc affecting its
21 properties.

22 What do you mean by that?

23 A. So whether it's fibrous enough,
24 platy, fibrous. Whether it is particle sizes
25 of less than 10 microns, less than 5 microns,

1 greater than 75 microns. There's
2 different -- certain pieces of literature
3 deal with different size ranges of talc. The
4 smaller the size range, the more toxic it is,
5 for example, to lung tissue; the more likely
6 it is to be able to move, based upon the
7 size, versus being engulfed by a macrophage
8 if it's a larger particle, things like that.

9 Q. So focusing specifically on
10 ovarian cancer, what role does size and
11 structure of a talc particle play with
12 respect to a risk of ovarian cancer in your
13 opinion?

14 A. I don't think I formed a
15 opinion that it has to be a specific size or
16 structure, because the -- my opinions are
17 related to the fact that we have a complex
18 mixture of ingredients within the body
19 powder, and my assessment's been on the
20 overall consumer product, not on any one
21 particular ingredient only within it.

22 So it's the idea of just
23 understanding that size and structure of
24 these particles are general principles that
25 affect toxicology. So a larger particle or a

1 fibrous particle may have a different tissue
2 toxicity response than a smaller particle.

3 So in other words -- I think I
4 discuss this later in a paragraph about
5 pleurodesis, the idea that you can get acute
6 versus chronic inflammation, or respiratory
7 distress or not. So it's just this idea of a
8 general principle that outlines how you would
9 think about particles generally as a
10 toxicologist.

11 Q. Well, okay. So you said that
12 your assessment is based on the overall
13 consumer product. That would be Johnson's
14 baby powder or SHOWER TO SHOWER®, correct?

15 A. Yes.

16 Q. All right.

17 A. Or Shimmer. I think that's the
18 other name. There's a third product.

19 Q. Okay. But my question to you
20 is, you actually cite a number of pieces of
21 literature in the section about the alleged
22 toxicity of talc that don't relate to the
23 overall consumer products at issue in this
24 case, correct?

25 MS. PARFITT: Objection. Form.

1 THE WITNESS: No, I would
2 disagree with that when you use the
3 word "relate." Relate to me means is
4 it relevant to the assessment, and
5 they are, even if they're not just on
6 the finished product.

7 But if what you mean is that
8 there are studies that did not test
9 the consumer product but individual
10 ingredients or -- that is true, yes,
11 but all of that is relevant or relates
12 to the overall risk assessment.

13 QUESTIONS BY MS. BRANSCOME:

14 Q. Okay. So given your view that
15 information about the individual constituents
16 is relevant to evaluating the overall
17 toxicity of the ultimate consumer products,
18 then my question to you is: How does the
19 structure and size of the component talc
20 particles play a role in toxicity with
21 respect to ovarian cancer?

22 A. Just generally -- it's not
23 just -- well, with respect to ovarian cancer,
24 we start with irritation, inflammation
25 potential. Size of particles and shape are

1 known to affect tissue toxicity as far as
2 adverse events like inflammation and/or
3 irritation.

4 Q. Okay. So that's -- that's what
5 I'm trying to understand in more detail.

6 What is your opinion with
7 respect to -- let's take size to start with.
8 Is there a particular size talc particle that
9 is more or less likely to cause inflammation,
10 in your opinion?

11 A. It depends whether you're
12 talking about acute or chronic. I would say
13 for acute inflammation the larger particles,
14 such as some of the particle sizes that are
15 used in the pleurodesis products, are more
16 likely to initiate an acute inflammatory
17 response due to the fact that they're large
18 enough that the body will recognize them with
19 a fairly robust foreign body response.

20 Q. What is your definition of
21 large?

22 A. So the literature varies, but
23 certainly particles that are above -- some of
24 the literature talks about particles that are
25 in the range of 25 to 75. Some of them talk

1 about larger particles even than that.

2 It has to do with the fact
3 that -- this is complicated by the fact that
4 any consumer product -- or any talc sample
5 will have a range of sizes because they don't
6 select for one size. They select for smaller
7 than. So a 200 mesh, a 400 mesh, that has do
8 with what will filter through.

9 So pleurodesis, they try to
10 avoid for those products the really small --
11 large amounts of less than 10 because that
12 leads to respiratory distress, whereas many
13 of the consumer talc products are using much
14 smaller, finer particles to get that feel and
15 performance they want from the consumer body
16 powders.

17 Q. Have you reviewed -- focusing
18 specific on Johnson & Johnson's products,
19 have you reviewed the documents that relate
20 to the specifications for the Johnson's
21 products with respect to the size of the
22 plate particles?

23 A. I have seen those, yes. I
24 can't tell you what each of them says without
25 pulling them out, but, yes, that is certainly

1 documents I have seen and relied upon.

2 Q. Is it consistent with your
3 understanding that it was Johnson & Johnson's
4 intention to select large platy talc
5 particles for its products?

6 MS. PARFITT: Objection to
7 form.

8 QUESTIONS BY MS. BRANSCOME:

9 Q. Have you seen that in the
10 documents?

11 A. I don't know that it's
12 described quite that way, but they certainly
13 were doing a 200 mesh selection. So -- for
14 their body powders products. So -- and they
15 were trying -- and they did make attempts to
16 look for sources that were more platy talc
17 than other forms, but that doesn't ensure
18 that everything is platy talc.

19 Q. Are you familiar with the term
20 "fines"?

21 A. Yes, generally, but I'm not --
22 but I'm not an expert in the processing of
23 talc as far as how you would go about
24 choosing an ore or a mine. There's others
25 that will be addressing that. That's not my

1 area.

2 Q. What is your understanding of
3 the term "fines"?

4 A. My understanding of the term
5 "fines" has to be looking for a sample or a
6 group that has been processed such that it
7 has certain characteristics.

8 Other than that, I would refer
9 you to the individuals in litigation that are
10 going to be dealing with the processing.

11 Q. Okay. Have you taken into
12 account in your analysis in any way the
13 beneficiation process that occurs between the
14 time that the talc is mined and it ends up in
15 one of the consumer products that is relevant
16 to your analysis?

17 MR. MEADOWS: Objection.

18 THE WITNESS: So what do you
19 mean by taking it into account? Am I
20 aware that they have something that's
21 in place for that? Yes.

22 But take into account, what do
23 you mean by that?

24 QUESTIONS BY MS. BRANSCOME:

25 Q. Are you familiar with the

1 effects that beneficiation can have on the
2 level of the component -- the components in
3 talc and what ultimately ends up in one of
4 Johnson & Johnson's consumer products?

5 MR. MEADOWS: Objection.

6 THE WITNESS: So I'm not -- I'm
7 not familiar with all the details, but
8 I am familiar that it is a process
9 they're using to attempt to result in
10 a product that has characteristics
11 that would be desirable for a consumer
12 product.

13 Again, there is my
14 understanding that others are going to
15 be discussing the geology or the
16 processing, and that is not something
17 I'm looking at.

18 The literature as it relates to
19 what has been tested in the public
20 literature in particular, and that
21 would be either an ingredient or a --
22 or a consumer product or a -- they may
23 discuss exposure occupationally to
24 mining or milling, which is -- which
25 is an issue that you can consider when

1 you're reviewing that literature as
2 well.

3 QUESTIONS BY MS. BRANSCOME:

4 Q. Okay. And so when you cite --
5 for example, you have a significant number
6 of -- I'm trying to find the right paragraph.

7 You have a section in your
8 report where you discuss a number of
9 different articles that relate to talc, and
10 in parentheses you identify that the talc
11 source might be cosmetic, it might be
12 industrial, things of that nature, correct?

13 A. Yes, I do that on purpose
14 because I wanted -- I did look at the
15 literature to understand what they were --
16 what they were -- what type of exposure they
17 were describing.

18 Q. Okay. And so understanding
19 that some of those products are not
20 representative of what ultimately is in
21 Johnson's baby powder, do you have anything
22 in your report that explains how you did or
23 did not give weight to those particular
24 studies?

25 MS. PARFITT: Objection. Form.

1 THE WITNESS: Let me look and
2 see what I say.

3 If the question has to do with
4 numerical rankings, no, I did not do
5 that. But you're asking something
6 else, right, broader than that,
7 correct?

8 QUESTIONS BY MS. BRANSCOME:

9 Q. The question that I have is,
10 how did -- is there somewhere in this report
11 that I can understand the weight that you
12 assigned to say a study that related to
13 industrial talc as opposed to information
14 about cosmetic talc, for example?

15 MR. MEADOWS: Objection.

16 THE WITNESS: So I -- I'm -- I
17 believe I address that. I don't know
18 it's exactly answering your question,
19 but I lay out for you the
20 characteristics of the literature in
21 paragraph 37, and I point out that the
22 scientific literature varies.

23 And the fact -- and I point --
24 and I admit -- I'm not admitting. I'm
25 stating the fact that in some cases

1 the authors will not describe it
2 specifically as the type of talc, but
3 just talc, whereas -- with no
4 description of purity or state, for
5 example. But in cases where the
6 literature does, I did consider that
7 in my weight of the evidence.

8 So, for example, when I -- when
9 I lay it out here in these bullets
10 where I'm putting for you tremolite
11 mining industrial grade cosmetic, it
12 certainly is something that I weighed.
13 And obviously as much information as I
14 can get on cosmetic-grade talc is
15 going to be most important in the
16 assessment, but that doesn't mean the
17 other information isn't relevant.

18 You want me to explain why?

19 QUESTIONS BY MS. BRANSCOME:

20 Q. Well, so, for example, you
21 describe the Dreessen article that related to
22 trimellitic talc that's mined out of
23 New York.

24 You would agree that
25 trimellitic talc from New York is not

1 something that ever ended up in Johnson's
2 products, correct?

3 MR. MEADOWS: Objection.

4 THE WITNESS: I don't think I
5 can answer that yes or no. I haven't
6 done an assessment to see whether it
7 ever ended up in the products. That's
8 a different question.

9 I certainly am aware of the
10 fact that was not a primary source of
11 their talc, that is true. I do know
12 that.

13 In other words, I don't have
14 records from -- going back from 1894
15 on what the source of their talc was.
16 So I can't tell you over time.

17 What I do know, what's been put
18 into depositions and testimony of
19 company employees more recently, where
20 it's my understanding that the
21 principal sources over the years were
22 either the Vermont mine, the Italian
23 mine or the Chinese mine. And there
24 were different interruptions in time
25 where different mines were used,

1 depending on sourcing.

2 QUESTIONS BY MS. BRANSCOME:

3 Q. So as part of your expert
4 analysis where you are evaluating articles
5 that relate to different types of talc from
6 different sources of talc, have you done an
7 analysis of how those particular types of
8 talc do or do not relate to what is in the
9 consumer product manufactured by Johnson &
10 Johnson?

11 MS. PARFITT: Objection. Form.

12 THE WITNESS: The first part of
13 your question, again? I'm sorry.

14 MS. BRANSCOME: Would you read
15 it back?

16 THE WITNESS: Could you read it
17 back to me again? I didn't mean to
18 wander, but the first few words I
19 missed.

20 (Court Reporter read back
21 question.)

22 THE WITNESS: Okay. So I
23 certainly did, which is why I'm
24 breaking this out here for you this
25 way.

1 So I am -- I am certainly
2 recognizing, and I analyzed on the
3 paper -- through the papers what type
4 of product, if available, that the
5 data is on.

6 But if you read my report in
7 the process of risk assessment, all of
8 these categories of papers are
9 relevant to telling you something
10 about what talc can do. And then when
11 you talk about drawing final
12 conclusions, I'm looking for
13 information, if I can, and I have it,
14 that is on point to the product that
15 was sold.

16 So certainly the studies that
17 give me information on cosmetic-grade
18 talc are extremely important to my
19 assessment, and they're ones that I've
20 discussed or we've even used in trial
21 before when we've talked about putting
22 together a timeline.

23 That's what this is about, by
24 the way. This discussion here, I'm
25 starting to lay out what information

1 was available over time, and that's
2 simply what this is. It's a survey of
3 the literature that talks about
4 adverse effects of talc, and if I can,
5 I separate it into different qualities
6 or purities.

7 QUESTIONS BY MS. BRANSCOME:

8 Q. Dr. Plunkett, respectfully, I
9 don't believe you answered my question.

10 Can you point me to anywhere in
11 your expert report that's been produced in
12 this MDL where you do an analysis of how the
13 different talc types and sources that you are
14 citing as support for the toxicity of talc
15 generally relate to the products manufactured
16 by Johnson & Johnson?

17 MR. MEADOWS: Objection.

18 THE WITNESS: So I don't know
19 how else to answer that but to tell
20 you I think that's what this whole
21 section is about. I step you
22 through -- I identify different types
23 of evidence. I identify for you what
24 was tested in those different pieces
25 of evidence, and then I step through

1 that to draw conclusions based upon
2 what was available for me to assess.

3 QUESTIONS BY MS. BRANSCOME:

4 Q. Okay.

5 A. I don't know how else to answer
6 it for you. That's what the section is meant
7 to do, and that's why I broke it out that
8 way. You know, I recognize that there is
9 data on different things.

10 What's interesting about even
11 the data on different things, there's a
12 common mechanism that is involved with the
13 type of tissue toxicity you get, and that's
14 irritation and inflammation. Regardless of
15 whether it is of a certain grade or not, you
16 get certain types of adverse reactions. May
17 be a more sustained reaction with a
18 industrial grade versus cosmetic grade, but
19 they all have the capability to produce that
20 type of adverse effect.

21 Q. Dr. Plunkett, where can you
22 point me to in your report that you discuss
23 the weight that you give studies that relate
24 to talc from New York as opposed to studies
25 that relate to cosmetic talc that ultimately

1 ended up in Johnson's baby powder?

2 MS. PARFITT: Objection. Form.

3 THE WITNESS: I've tried to
4 answer that for you. The weight that
5 I'm giving -- the weight that I'm
6 giving is part of my assessment. So,
7 again, I don't give numerical
8 rankings. I've answered that for you.
9 I don't do that.

10 What I instead do is I'm
11 looking at everything that's relevant,
12 everything that's available. I do
13 categorize it, so I am selecting -- I
14 am identifying or analyzing the
15 information for what it describes.
16 And then if you go further on down, I
17 try to tell you what I think is
18 important about that information.

19 The overall conclusions I'm
20 drawing in the report, though, when I
21 cite to specific studies in the risk
22 assessment, the majority of those
23 studies I believe that I'm citing for
24 you, outside of notice, have to do
25 with -- that's more of a warnings

1 issue -- have to do with the issue of
2 cosmetic talc. Because the human
3 studies are describing cosmetic talc.
4 The NTP studies is a pure talc. Many
5 of the in vitro studies and other
6 animal studies are looking at,
7 quote/unquote, a talc that is not an
8 industrial grade or from a mine that
9 would have -- be looked at in that
10 way. So --

11 QUESTIONS BY MS. BRANSCOME:

12 Q. You understand that there are
13 different types of cosmetic talc, correct?

14 A. Yes, I am aware.

15 Q. And cosmetic talc can be mined
16 from a number of different mines globally,
17 correct?

18 A. That's correct.

19 Q. And some of the studies that
20 you cite in your report are testing cosmetic
21 talc from other consumer products, for
22 example, Cashmere Bouquet, correct?

23 A. Some. The majority of them are
24 not, but I would agree that some do, yes.

25 Q. Okay. Have you done an

1 analysis of how the talc that is used in
2 Cashmere Bouquet, for example, relates to the
3 talc that is used in Johnson's baby powder?

4 Is that an analysis that you
5 have done before relying on that information
6 in your report?

7 MR. MEADOWS: Objection.

8 MS. PARFITT: Objection.

9 THE WITNESS: My analysis -- I
10 did do an analysis to look at what was
11 described, what products are
12 described, but I certainly -- I
13 certainly did not throw out studies
14 that described Cashmere Bouquet
15 because I would -- I still believe as
16 a toxicologist and a risk assessor
17 that those types of products are
18 important to the overall weight of the
19 evidence about the hazard and the
20 risks posed by talc.

21 You know, I just -- I just -- I
22 guess I disagree with you if you're
23 saying they're irrelevant. I don't
24 believe that they are.

25

1 QUESTIONS BY MS. BRANSCOME:

2 Q. I was simply asking: Did you
3 do an analysis that would allow you to
4 compare the ingredients in another product,
5 like consumer Cashmere Bouquet, before you
6 rendered an opinion with respect to Johnson's
7 baby powder based on tests of Cashmere
8 Bouquet? Did you do that analysis?

9 MR. MEADOWS: Objection.

10 THE WITNESS: I do not have
11 access to internal company documents
12 for the manufacturers of Cashmere
13 Bouquet, so I certainly couldn't do
14 the analysis in the same way that I
15 can do it here, where I can identify
16 what Johnson & Johnson and Imerys
17 describe as sources of the talc that
18 was used for the Johnson & Johnson
19 baby powder, without --

20 QUESTIONS BY MS. BRANSCOME:

21 Q. So you have no way of knowing
22 one way or the other whether that talc is
23 similar, correct?

24 MR. MEADOWS: Objection.

25 MS. PARFITT: Objection.

1 THE WITNESS: Well, I think I
2 do know it's similar, if you look on
3 the bottle as far as what is described
4 it being, but if you're asking me --
5 if you're asking did we fingerprint it
6 to only a particular mine, this is the
7 beauty of the data. The data shows
8 that regardless of the type of product
9 you're looking at, there's consistency
10 across the study.

11 So -- but I did not try to
12 segregate out studies that only dealt
13 with Cashmere Bouquet, no, I did not
14 do that.

15 QUESTIONS BY MS. BRANSCOME:

16 Q. Okay. As you sit here today as
17 a toxicologist, is it your position that
18 industrial-grade talc that might contain up
19 to 70 percent tremolite presents the same
20 level of toxic effect as cosmetic talc that
21 may contain no tremolite or tremolite at a
22 very, very low level?

23 MS. PARFITT: Objection. Form.

24 THE WITNESS: I haven't formed
25 that opinion, no.

1 QUESTIONS BY MS. BRANSCOME:

2 Q. Okay. And so have you formed
3 an opinion that I could find in your report
4 that discusses in any way the relative
5 toxicity of different types of talc?

6 A. That, you may find. I need to
7 go back and look how I set it out, but I
8 think I -- I talked with you about the
9 difference between fibrous versus platy. I
10 do discuss that.

11 And I talk about the problems
12 when you have a complex mixture that has
13 added to it things like asbestos and heavy
14 metals, because I talk about the additivity
15 issue that can come to play. So that -- in
16 other words, increased risk when you have a
17 complex mixture with additional components
18 that all share the same toxic properties as
19 far as target organs or types of effects or
20 mechanisms that are triggered in the body.
21 That's what I point you to.

22 I -- I don't -- that's the only
23 way I can answer that for you, I think, based
24 on what I know I have in here.

25 Q. Okay. You talk about the term

1 "asbestiform talc."

2 You talk about asbestiform

3 talc.

4 Are you familiar with that?

5 A. I do mention that in my report,

6 yes.

7 Where are you?

8 Q. At paragraph 30. It's on

9 page 19 of your report.

10 A. Yes, I'm here.

11 Q. Okay. And the first sentence

12 in paragraph 30 you state, "In the published

13 medical literature, there is often discussion

14 of talc using terms such as fibrous talc,

15 asbestiform talc, non-asbestiform talc or

16 tremolite."

17 Do you see that?

18 A. Yes, I do.

19 Q. Okay. Is it your opinion that

20 tremolite is a form of talc?

21 A. So tremolite is a -- is a -- is

22 a type of fiber or a -- tremolite is a -- is

23 a substance or a entity that has been

24 identified as a specific morphology, I guess,

25 identified characteristics of a -- it has

1 identified characteristics.

2 There's -- within the
3 asbestos -- the asbestos literature
4 there's -- it's one of the forms -- forms of
5 asbestos that's described. For example, in
6 IARC, they describe all of the ones that have
7 carcinogenic properties. It's one of them.

8 Within the literature within
9 Johnson & Johnson's documents, there's
10 tremolite discussed as -- I assume them
11 referring to asbestos tremolite, asbestos in
12 a tremolite characteristic. I have seen
13 tremolite talc also mentioned in the
14 literature.

15 If you want a specific
16 discussion of each of those, again,
17 there's -- I understand there's experts that
18 are going to describe the distinguishing
19 characteristics of each of those.

20 I'm only setting out this is
21 what I have seen, talked about, in the
22 literature.

23 Q. So you are not an expert on the
24 differences between fibrous talc, asbestiform
25 talc, non-asbestiform talc and tremolite as

1 it relates to toxicity. Is that your opinion
2 today?

3 A. No, that's not what I'm saying.
4 I'm saying that if you want me to -- I'm --
5 if you want me to describe the
6 characteristics and the morphology of each of
7 those individually, that's something a
8 geologist would do.

9 But certainly as far as the
10 toxicity assessment I did, each of these
11 types of -- each of these words, I guess, or
12 names have been applied in the literature
13 when they talk about toxicity of talc. Some
14 of the literature talks about fibrous talc or
15 just -- other literature just talks about
16 talc. Some of it, for example, the IARC
17 monographs, distinguish between asbestiform
18 talc and non-asbestiform talc in their
19 assessments of the cancer risk.

20 And then tremolite is discussed
21 as a component of talc. And I have seen
22 papers that talk about tremolite --
23 nontremolite talc or tremolite-containing
24 talc. That's how you most often see it.

25 So it's the idea that it is a

1 constituent of certain mines that -- and
2 that's my understanding of it. But if you
3 want -- and they all -- they all certainly do
4 show that the toxicity can be affected,
5 whether it's a fiber or a platy particle. So
6 tremolite being a fiber would certainly
7 affect my overall assessment of risk. The
8 more tremolite that you would have would
9 make -- would make it more likely to be
10 reactive in terms of a foreign body response,
11 depending on the size.

12 Q. What's your basis for saying
13 that?

14 A. That's based on a fibrous form
15 versus a platy particle form. That's the
16 issue of -- I have that paragraph where I
17 talk about what macrophages look for, can
18 engulf or not engulf. So those are all
19 things that are important to a toxicologist
20 to understand exist.

21 But certainly within my
22 assessment I have to include literature from
23 all of those because of the fact that all of
24 those are relevant to the toxicity profile,
25 since I know that the cosmetic baby powders

1 and the data I've seen shows detection of
2 something called fibrous talc.

3 I see detection of tremolite
4 within certain samples of baby powder.

5 And then I have just the
6 general category of asbestiform versus
7 non-asbestiform when I consider the way, for
8 example, IARC has reviewed the
9 carcinogenicity.

10 So those are -- those are terms
11 that I'm laying out because I think they are
12 something you need to understand exists in
13 the literature.

14 Q. Okay. But I'm trying to
15 understand, not helping me understand the
16 literature. I'm trying to understand your
17 opinions with respect to toxicity.

18 Is it, for example, your
19 opinion that fibrous talc has the same toxic
20 potential -- let's focus specifically with
21 respect to ovarian cancer -- as tremolite?

22 A. I haven't formed that opinion,
23 but, again, I would -- my opinion has been
24 formed on the fact that we have complex
25 mixture that includes all of these things.

1 Q. Okay. And so when you're
2 looking at a complex mixture, you would agree
3 as a toxicologist it would be important to
4 understand the constituent elements of that
5 mixture, correct?

6 A. Yes, it is important to
7 understand that this is -- what is in the
8 mixture, and that's -- that's part of what I
9 try to do.

10 Q. Okay. And it would be
11 important before drawing conclusions from one
12 study that might have different constituent
13 components, it's important to understand the
14 relative toxicity of individual constituent
15 elements, correct?

16 A. Depends if you can or not. I
17 mean, there's certain types of studies you
18 can, where in the published literature that's
19 been described. That's why I'm pointing this
20 out. It's the idea that within the
21 literature, when you go through, it's
22 important to understand what you can say
23 about the consistency across the literature
24 where maybe different types of talc are
25 discussed.

1 And that's what I -- I think I
2 lay out for you. I tell you there's
3 consistency in certain toxic effects that are
4 seen. Regardless of the form that you're
5 looking at, talc has certain properties, and
6 all of these things are -- been shown to be
7 in the complex mixture, so I have -- as a
8 result, all of that literature has relevance
9 to at least the hazard part of my assessment,
10 and certainly have relevance to -- when you
11 want to talk about warning and the final risk
12 assessment, they're definitely relevant, but
13 certainly the -- when I go through this
14 process, I am trying to focus as much as I
15 can on a product that is most similar to the
16 one I'm assessing.

17 So obviously that's why --
18 that's one of the reasons I do look at the
19 human data, because the human data is
20 involving a consumer product use, which is
21 what I'm talking about here.

22 Q. Is it using specifically
23 Johnson's baby powder?

24 A. Many of them are, yes.

25 Q. Okay.

1 A. Based on my understanding of
2 what I see discussed within the literature.

3 Q. Did you identify in your report
4 specifically which report -- which studies
5 have used a consumer product manufactured by
6 Johnson & Johnson?

7 A. I haven't laid them out
8 individually, no, but I am aware of
9 discussions of this general issue within some
10 of the documents I've seen, and essentially
11 Johnson's body powders products were the
12 overwhelming share of the market.

13 Q. But you would agree that
14 studies that did not involve the consumer
15 product manufactured by Johnson & Johnson
16 should be given less weight when analyzing
17 whether or not there are risks associated
18 specifically with Johnson & Johnson's
19 products?

20 MS. PARFITT: Objection. Form.

21 MR. MEADOWS: Objection.

22 THE WITNESS: It depends on the
23 question being asked within the
24 assessment, the risk assessment. It
25 really does, I mean, because each of

1 these studies brings a piece of
2 evidence to the risk assessment.

3 And so the question is -- for
4 each one, you consider it on a
5 case-by-case basis. It is possible,
6 yes, that you would give less weight.
7 It's also possible that you would not,
8 dependent upon what you know about
9 that study and how it relates to other
10 studies that are out there.

11 QUESTIONS BY MS. BRANSCOME:

12 Q. So methodologically, how would
13 I understand from your report marked as
14 Exhibit 4 under what circumstances to give a
15 study that relates to, for example,
16 industrial talc less weight than a study that
17 actually used Johnson's baby powder?

18 MR. MEADOWS: Objection.

19 THE WITNESS: Well, I've tried
20 to tell you that. That's what I said
21 for you. That's why I am doing it. I
22 certainly am trying to focus in on
23 studies that deal with the consumer
24 product.

25 But what I find when I look

1 across the studies that are dealing
2 with not the consumer product but
3 other descriptions, there is a
4 consistency in the types of effects
5 you see.

6 And since I'm not quantifying
7 the risk but identifying it as being
8 increased or not, in other words, is
9 it more likely than not that someone
10 exposed in this way could be at a risk
11 of ovarian cancer, that's what I'm
12 talking about.

13 So again, it's -- if I was
14 trying to identify differences in
15 cancer potency factors for different
16 types, then, yes, if I had an animal
17 study on each of those, I could
18 compare potency for cancer, but that
19 hasn't been done.

20 QUESTIONS BY MS. BRANSCOME:

21 Q. Okay.

22 A. So instead, what I have to do
23 is rely on what is available to me. And
24 based on my judgment, that's how I review the
25 studies.

1 Q. And so for the opinions that
2 you are offering in the MDL, you agree that
3 you are not quantifying the risk associated
4 with Johnson's baby powder, SHOWER TO SHOWER®
5 or Shimmer with respect to the potential for
6 causing ovarian cancer?

7 MS. PARFITT: Objection. Form.

8 THE WITNESS: In terms of a
9 cancer potency factor, that is true, I
10 am not. Instead, what I am doing is I
11 am quantifying whether or not I
12 believe that the risk is increased
13 above a background risk.

14 That has to do with -- that's
15 where I bring in, in my risk
16 assessment, the human data, because
17 the human data is showing
18 statistically significant increases in
19 risk in populations using the consumer
20 product.

21 So I have a quantification
22 where I'm using the word "increased,"
23 and I believe to a reasonable degree
24 of medical certainty that indeed the
25 risk is increased. So I'm quantifying

1 in that way, but I'm not giving it a
2 number. I'm not saying that the
3 cancer potency factor is such that you
4 increase the risk from one in a
5 million to 10 in a million to 1 in a
6 thousand. That I have not done
7 because I don't have the data, the
8 studies. The company has not done
9 studies on each of these to allow me
10 to do that.

11 QUESTIONS BY MS. BRANSCOME:

12 Q. Okay. The reference that you
13 made to the human data that you believe shows
14 a statistically increased risk in populations
15 using the consumer product, have -- which --
16 have you identified in your report which of
17 those studies are specifically using a
18 product that was manufactured by Johnson &
19 Johnson?

20 A. I don't lay that out for my
21 report, I do not, but certainly it is
22 something that for some of the studies I
23 believe you can -- you might be able to get
24 some of that information from. But certainly
25 I have not laid that out individually in my

1 report, no.

2 Q. And you would agree that for
3 some of those studies there is no information
4 as to the specific type of consumer talc that
5 the individuals who are being studied used,
6 correct?

7 MS. PARFITT: Objection. Form.

8 THE WITNESS: I would agree
9 that in some of those studies they're
10 not saying, but that is why you look
11 at the evidence overall.

12 And what's important to look at
13 in terms of now -- if you wanted to go
14 to Bradford Hill, that's why you look
15 at things such as consistency. So
16 what do the studies show. We see a
17 certain level of increased risk across
18 studies, regardless of who did the
19 study or what population was being
20 looked at.

21 So that's the best way I can
22 answer that for you. That is -- that
23 is part of the -- of the assessment
24 that you look at.

25

1 QUESTIONS BY MS. BRANSCOME:

2 Q. In reaching your opinion in the
3 MDL that there is an increased risk above
4 background of ovarian cancer from the use of
5 products manufactured by Johnson & Johnson,
6 have you made an attempt to identify
7 specifically which studies, the human studies
8 on which you rely, test or look at people who
9 have used Johnson & Johnson's products?

10 MS. PARFITT: Objection. Form.

11 THE WITNESS: It's my -- my
12 review of the study indicates that I
13 would say for the vast majority of
14 them you cannot do that.

15 But you can take what is
16 reported and look at things such as
17 market share and those kind of things
18 to get an idea of what you believe the
19 exposure would have been.

20 But certainly I have not -- I
21 have not tried to apply some kind of a
22 numerical value to how many people in
23 the study may have used Johnson's baby
24 powder or not, no, that has not been
25 done. I don't think anybody -- any of

1 the bodies that have looked at this
2 have done that.

3 QUESTIONS BY MS. BRANSCOME:

4 Q. You have not done a market
5 share analysis, correct?

6 A. No, I've seen this in documents
7 only. I have not done my own. There are
8 company documents that talk about their
9 market share.

10 Q. Okay. Have you made an attempt
11 to examine the levels of fibrous talc or
12 asbestiform talc that are in different
13 consumer products, aside from Johnson's baby
14 powder or SHOWER TO SHOWER® or Shimmer?

15 A. So for that are you referring
16 to things such as -- other types of cosmetics
17 like foundations or lipsticks or --

18 Q. I'll rephrase.

19 Have you made any attempt to
20 examine whether other cosmetic talc body
21 powders have a different percentage of
22 fibrous, or what you refer to as asbestiform
23 talc, from the Johnson & Johnson products?

24 Have you done any analysis to
25 make that comparison one way or the other?

1 MS. PARFITT: Objection. Form.

2 THE WITNESS: I certainly
3 haven't done -- I certainly didn't do
4 a directed analysis to try to
5 determine that, but there is
6 information, I believe, in -- I think
7 if you look at some of Dr. Longo's
8 work, that may be there.

9 And I believe in Dr. Blount's
10 published paper there may be a
11 discussion of the type of powder
12 product used, where she was looking
13 for -- at least for asbestiform --
14 asbestos within the talc. It may be
15 tremolite as well, but -- if you want
16 me to look, I can do that. I just
17 don't recall whether -- I think she
18 did talk about sources of the talc,
19 where it came from, so...

20 QUESTIONS BY MS. BRANSCOME:

21 Q. Okay. But as you sit here
22 today, you can't point me to any analysis
23 that you did or an analysis that you relied
24 on that would relate different brands of
25 cosmetic talc body powders with respect to

1 their constituent components?

2 MS. PARFITT: Objection.

3 Completely misstates her testimony.

4 She mentioned Dr. Blount. She

5 mentioned others.

6 THE WITNESS: So I think what I
7 started with, I said I haven't done a
8 directed analysis to try to determine
9 specifically how this product versus
10 this product versus this product may
11 have looked over time, because I don't
12 have access to a full data to do that.

13 But what I do have is data that
14 has -- I do see published data, for
15 example, Blount and maybe some of the
16 other published studies, that looked
17 at this issue, at least of asbestos
18 presence in talc. And I believe
19 Dr. Longo also had things that weren't
20 just Johnson's. I believe he had
21 Cashmere Bouquet, for example, samples
22 in some of the things he looked at.

23 So I can point you to those
24 things that I have reviewed, but I
25 haven't -- there's nowhere in here

1 that I state for you that it's my
2 opinion that Cashmere Bouquet has this
3 specific pattern of constituents as
4 compared to Johnson & Johnson's. No,
5 I have not done that.

6 QUESTIONS BY MS. BRANSCOME:

7 Q. Okay. And that would be true
8 for any other brand of cosmetic talc, body
9 powders, Jean Nate, Lily of the Valley, not
10 just Cashmere Bouquet, correct?

11 MS. PARFITT: Objection.

12 THE WITNESS: That is correct,
13 I don't have access to that
14 information.

15 QUESTIONS BY MS. BRANSCOME:

16 Q. Have you done any analysis of
17 the constituent components of talc and how
18 they have changed even within Johnson's --
19 Johnson & Johnson's manufactured products,
20 how the constituents of the consumer products
21 may or may not have changed over time?

22 A. I've done some of that, yes,
23 and I laid that out, I think, for you, when I
24 talk about the differences in the products
25 that are described within the documents, the

1 company documents, from the '70s versus the
2 '80s versus later on, as far as the changes
3 that were made to specifications of the
4 product, for example. That's something --
5 and I think I've talked about that a bit at
6 trial as well.

7 Q. Okay. And is it your view that
8 the risk potential for Johnson & Johnson's
9 manufactured products have changed at all
10 over time with respect to ovarian cancer?

11 MS. PARFITT: Objection.

12 THE WITNESS: I have not -- I
13 have not attempted to differentiate a
14 risk potential at only one point in
15 time.

16 What I have done over points of
17 time is looked at the issue of
18 warnings and what should be warned
19 about.

20 But my analysis related to the
21 hazard or the risk assessment of the
22 products is considering all of the
23 available information, which would be
24 all of that information over time.

25

1 QUESTIONS BY MS. BRANSCOME:

2 Q. Okay. You talk about, in
3 paragraph 35 primarily -- we'll talk about
4 the fragrance components in more detail, but
5 you talk about the idea of chemicals being a
6 potential irritant.

7 Are you familiar with that?

8 A. Yes, that's correct.

9 Q. Is it your position that any
10 product that contains chemicals that could be
11 an irritant should be labeled with a health
12 warning?

13 MS. PARFITT: Objection.

14 MR. MEADOWS: Okay.

15 THE WITNESS: I don't think
16 that's -- no, I don't think I've
17 formed that specific opinion.

18 But the opinion that I think
19 I'm expressing here is that when you
20 have a -- the information that I have,
21 which unfortunately the company hasn't
22 given us percentages or actual levels,
23 instead, what I do as a toxicologist,
24 I look at what is there. And when I
25 see over a hundred chemicals there,

1 that 70 percent of them have been
2 linked as an irritant hazard, there is
3 the issue of toxicological additivity
4 to consider.

5 So certainly as a risk
6 assessor, when I have that many
7 potential sources of irritation as far
8 as chemicals going into a complex
9 mixture, certainly I think I have
10 formed the opinion that I think that
11 is something that needs to be
12 considered when you're talking about
13 providing information to consumers,
14 yes.

15 QUESTIONS BY MS. BRANSCOME:

16 Q. As a toxicologist, would it be
17 important to you to understand the exact
18 percentages of all of the constituent
19 components of, say, Johnson's baby powder,
20 for example?

21 A. Are you talking about just the
22 fragrance or are you talking about everything
23 that's in it?

24 Q. Dr. Plunkett, you referenced
25 the fact that the company has not provided

1 you with specific percentages, and so I'm
2 asking you, is that something that as a
3 toxicologist would be important information
4 to you?

5 A. Depends. Certainly with the
6 fragrance -- and I'm talking about the
7 conversation about this paragraph is focusing
8 on the fragrance components.

9 So, yes, I mention that it
10 would be nice to know, it would be good to
11 know, if we could, exactly what was in there,
12 because I could quantify the hazard or
13 quantify the risk, actually. So instead, I
14 have -- I identify it as a hazard, but I
15 can't quantify it without those levels.

16 But does that change -- make a
17 difference in the overall conclusions I draw?
18 No, it doesn't affect the overall conclusions
19 that I have drawn, but it adds that other
20 piece of the puzzle that deals with the fact
21 that we have a complex mixture that have a
22 combination of ingredients that target
23 irritation.

24 And irritation and the
25 potential to produce an inflammatory

1 response, in my -- if you've read my report,
2 you understand that I think that's a key
3 factor in increasing the risk for ovarian
4 cancer.

5 Q. Understanding the percentages
6 of the constituent components, is that
7 limited only to fragrance, or would it also
8 be important to understand the percentages
9 for the heavy metals that you contend are in
10 Johnson's baby powder?

11 A. So if I was trying to define
12 the hazard of each component, I would
13 certainly want one to know that. As a
14 result, what I'm doing instead is looking at
15 the complex mixture. In other words, this is
16 a mixture of all these things.

17 I break out those individual
18 components, or constituents, to tell you
19 about the hazard that is brought to play or
20 the toxicity profiles that exists. And
21 what's important about that in my overall
22 evaluation of the end product, which is what
23 my risk assessment is based on, the end
24 product, shows that I have multiple
25 components with similar types of effects.

1 And as a toxicologist, when you do that, that
2 affects the conclusion that you can draw
3 about a body of literature.

4 Q. Okay. You do understand that
5 there is testing data available about the
6 percentages of the constituent components
7 with respect to heavy metals, et cetera, that
8 have been in Johnson's baby powder over time,
9 correct?

10 A. There is some information.
11 Unfortunately, the information is not
12 complete as to every lot or every sample, as
13 far as what I have seen. And also, there's
14 some -- some of the sampling is reported as
15 more of a limit versus an actual
16 quantification. So it depends upon which --
17 which result, study result or document,
18 you're looking at.

19 There is some there, yes, and
20 that's one of the reasons why I identified
21 these as part of my risk assessment, because
22 I look for a pattern of these metals that are
23 known to carry a hazard and whether or not
24 these are ones I'm seeing detected time and
25 time again.

1 Q. But you made no attempt to
2 quantify the risk with respect to any of
3 those components or use that data in any way,
4 correct?

5 MS. PARFITT: Objection. Form.

6 THE WITNESS: No, I used
7 that -- that data as part of -- my
8 risk assessment as part of my hazard
9 assessment, absolutely. It's part of
10 the hazard assessment.

11 But as far as quantifying them
12 individually, no. I am quantifying
13 the risk and looking at the risk of
14 the entire product, not of just one
15 individual component of the product.

16 QUESTIONS BY MS. BRANSCOME:

17 Q. Well, we already discussed
18 you're not quantifying the risk with respect
19 to the entire product, correct?

20 A. Well, I'm quantifying it in
21 terms of an increase above background, which
22 I'm not giving you a -- I told you I wasn't
23 giving you a cancer potency factor. That is
24 true. That I am not doing.

25 But I am quantifying it by

1 using a word such as an increase -- an
2 increased risk.

3 Is that a specific number? Am
4 I telling you that it's increased by two
5 times or four times or six times? No. The
6 data available did not allow us to do that,
7 with the exception of the epidemiological
8 data. And the epidemiological data can show
9 you that in that piece of evidence there
10 appears to be a 30 percent increased risk
11 above background.

12 Q. Did you make an attempt to
13 quantify the risk with the data that you had
14 available to you with respect to the final
15 consumer product?

16 A. I could not, based on the data
17 I had, because I didn't have a
18 well-controlled animal study to be able to
19 pull that out that way.

20 Instead, what I -- in this type
21 of weight of the evidence, you look at what
22 you might be able to quantify based on the
23 human data. And certainly the human data
24 showing the statistically significant
25 consistent findings across studies for that

1 30 percent increased risk, that is part of my
2 overall weight of the evidence for me making
3 the statement the risk is increased.

4 But you'll notice I don't say
5 increased risk of 30 percent, because I don't
6 believe that I can state that with certainty
7 in the way I do a risk assessment. But
8 certainly as any one individual -- any one
9 individual piece of evidence or any one body,
10 like the epi data, others have made -- other
11 bodies who have looked at the -- talked about
12 the consistency of the increased risk signal
13 in the epi studies as being in the range of
14 30 percent.

15 Q. Okay. But you would agree that
16 based on the methodology that you applied in
17 this case, you could not say to a reasonable
18 degree of scientific certainty that there is
19 an increased risk of, for example, 30 percent
20 with respect to use of Johnson's baby powder
21 and ovarian cancer, correct?

22 MR. MEADOWS: Objection.

23 THE WITNESS: I have not done
24 that. And I'm not saying that
25 somebody else couldn't do that. I

1 have not -- I have not chosen to do
2 that based on my evaluation of the
3 data.

4 QUESTIONS BY MS. BRANSCOME:

5 Q. And the same would be true if I
6 asked that question and substituted any
7 particular number, a 10 percent increased
8 risk, a 20 percent increased risk, correct?

9 MR. MEADOWS: Objection.

10 THE WITNESS: I haven't given a
11 specific number in my final opinions,
12 that is true.

13 QUESTIONS BY MS. BRANSCOME:

14 Q. Okay.

15 A. I've tried to explain to you
16 what evidence I do think is there, however.

17 Q. Now, we've talked about
18 different types of talc that might have
19 different constituent components, but you
20 also look at exposure to talc in an
21 occupational setting.

22 Do you recall that?

23 A. Some of the studies that I've
24 relied upon, yes, some of them were
25 occupational.

1 Q. Okay. And you understand that
2 in an occupational setting, you would agree
3 that the exposure, particularly via
4 inhalation, would be much higher than it
5 would be through the use of a consumer
6 product, correct?

7 A. It depends on the occupation,
8 but, yes. For example, I would agree a miner
9 would be expected to have that, but there are
10 certain, quote/unquote, occupational studies
11 where the exposure levels that -- for
12 example, there are -- I believe there's at
13 least one study that looked at application of
14 talc powders in -- maybe in a material,
15 coating materials in a factory. Those kinds
16 of studies would be different than a mining
17 study.

18 But, certainly, yes, I
19 understand that occupational studies, the
20 inhalation exposure is the pathway that would
21 be predominant versus in the consumer body
22 powder use, I'm talking about the predominant
23 exposure pathway in my opinion is going to be
24 through perineal use, even though inhalation
25 exposure can occur.

1 Q. Is it your opinion as you sit
2 here today that someone could develop ovarian
3 cancer through -- exclusively through the
4 inhalation of Johnson's baby powder?

5 MS. PARFITT: Objection.

6 THE WITNESS: I haven't formed
7 that opinion at this point in time.

8 QUESTIONS BY MS. BRANSCOME:

9 Q. Have you done any analysis or
10 can you point me to any analysis in your
11 report that makes a comparison of the
12 exposure levels that might be seen in an
13 occupational setting to what would be seen by
14 a consumer?

15 A. Are you asking me for a piece
16 of evidence that does that comparison, or is
17 there evidence that allows you to do that
18 comparison?

19 Q. Have you cited or discussed any
20 of the evidence or done an analysis in any
21 way that would compare exposure levels in an
22 occupational setting to what you would
23 anticipate a consumer using Johnson's baby
24 powder might be exposed to?

25 A. I don't think I did it as a

1 separate analysis, but as part of my analysis
2 I considered evidence that showed -- provided
3 me with such data. So, for example, if you
4 want, I can point you to a -- I have an
5 inhalation paragraph, I think.

6 Let me look for it real quick.
7 See if I can find it quickly for you. I
8 don't want to waste your time.

9 Q. Sure.

10 A. So there's -- I don't see it
11 cited here, but there's at least one document
12 I reviewed where the company themselves made
13 a comparison, and I have seen that, of
14 inhalation exposure to talc suspended in air
15 with diapering. Dr. Longo has done a
16 measurement of exposure in air with perineal
17 application of talc. So I'm aware of those
18 studies.

19 And then I certainly am aware
20 of the fact that those numbers are different,
21 or smaller, than many of the numbers I see
22 reported in some of the occupational studies.
23 But I can't say that's true for all.

24 I would certainly, though, say
25 that if you're just talking inhalation, I

1 certainly would expect a miner or a miller to
2 have a greater potential for inhalation
3 exposure than routine use of the consumer
4 product, with the exception of the studies --
5 the reports of large amounts of exposure in
6 children where the inhalation -- where they
7 were inhaling large amounts of powder.

8 And so that's a different
9 story. That's sort of an acute overdose
10 exposure, I guess, versus the typical daily
11 exposure through occupational or consumer
12 use.

13 Q. And that raises an interesting
14 question. You discuss health hazards
15 associated with talc being known, and in some
16 cases deaths had been reported.

17 You're aware that those relate
18 to asphyxiation deaths, correct?

19 A. Or long-term injury to lungs.
20 Maybe not an immediate asphyxiation, but lung
21 damage produced by large amounts -- some of
22 the children would go to the hospital and be
23 sick for a while and then die. So they
24 didn't asphyxiate immediately, right? But
25 some of them did. You're exactly right.

1 Both of those things occur, and
2 I address that also in my warning section
3 about the fact that that warning didn't --
4 was not put on the product for a long period
5 of time even though those types of reports
6 were coming in early.

7 Q. You would agree that that is a
8 completely different biologic mechanism than
9 what you are proposing the biological
10 mechanism is for ovarian cancer to develop
11 with respect to talc use, correct?

12 MR. MEADOWS: Objection.

13 THE WITNESS: I would agree
14 that it's an acute response versus
15 chronic, yes, that I agree with.

16 It's not entirely different in
17 some cases because some of the tissue
18 reactions you saw were indicative of
19 irritation when some of the lung
20 samples were looked at. But
21 certainly, yes, that's acute exposure
22 versus chronic exposure, and I'm
23 focusing on ovarian cancer on chronic
24 exposure scenarios.

25

1 QUESTIONS BY MS. BRANSCOME:

2 Q. Okay. Now, you would agree
3 that -- so let's set aside inhalation.

4 You agree that for talc -- for
5 Johnson's baby powder or another one of
6 Johnson & Johnson's consumer talc products to
7 reach an individual's ovaries, it must pass
8 from the perineum, through the vagina and the
9 cervical canal, move across the uterus -- and
10 again, it's the ciliary motion of the
11 fallopian tubes -- cross the peritoneal space
12 between the fimbriae and ovaries, escape
13 phagocytosis in the peritoneal space, and
14 then attach to the surface of the ovaries,
15 correct?

16 MS. PARFITT: Objection. Form.

17 MR. MEADOWS: Okay.

18 THE WITNESS: If the issue is
19 attaching to the surface, yes.
20 There's also some information
21 indicates the site of attack may be
22 actually at the fallopian tube exit to
23 the peritoneum. But, yes, that's
24 correct, there's been some discussion
25 in the literature on ovarian cancer

1 about whether the tumors are arising
2 in the tubes versus the ovaries.

3 But I would agree, I think
4 both -- I think both of those
5 things -- those things -- there is a
6 passage that has to happen, regardless
7 of whether the end point is at the
8 fallopian tube or at the ovary.

9 QUESTIONS BY MS. BRANSCOME:

10 Q. Okay. Is it your view that the
11 consensus has been reached that ovarian
12 cancer can be caused by talc landing in the
13 fallopian tubes?

14 A. I haven't formed that opinion,
15 though I do believe this will be discussed by
16 some of the other experts.

17 Q. Okay. Have you personally
18 conducted any tests or experiments to confirm
19 the theory that talc migrates from
20 application at the perineum to the ovaries?

21 A. If by that you mean something
22 where I performed a laboratory test myself,
23 no, I have not done that.

24 Q. As a toxicologist, are you
25 capable of doing that?

1 A. Yes, I believe if asked I
2 could -- I could attempt to design something
3 to look at that issue.

4 Q. Okay.

5 A. But I would argue that I think
6 it doesn't make a lot of sense to revisit
7 based upon what we already know from the
8 scientific literature and the review papers
9 from the gynecological community. I believe
10 it's -- it's understood that it can migrate.

11 Q. In your opinion, has an animal
12 model been successfully developed that would
13 allow the testing of talc migration in humans
14 from the perineum to the ovaries?

15 A. I think I tell that you in my
16 report. I believe that the human data is the
17 relevant data to look at this issue.

18 So it would be very difficult
19 to design a study to do this based on the
20 typical laboratory species that are used in
21 toxicology testing. Even -- even the monkeys
22 have issues, and the biggest issues with
23 monkeys is the ethicality of using a monkey
24 to settle -- to address a question that I
25 believe is settled within the gynecological

1 and scientific community.

2 Q. Now, you state in your report
3 that talc that's applied through perineal
4 use -- I believe the term you use --
5 routinely migrates to the ovaries.

6 Is that your opinion?

7 A. Are you reading from my report?

8 MR. MEADOWS: To the extent
9 that question is still lingering, I
10 object to it.

11 QUESTIONS BY MS. BRANSCOME:

12 Q. On paragraph 43 on page 29.

13 A. So I think as I've stated it,
14 the studies that I have reviewed demonstrate
15 that inert particles routinely move from the
16 lower female reproductive tract up into
17 fallopian tubes and towards the ovaries.

18 Q. What do you mean by routinely?

19 A. It's the percentages of
20 movement that are reported in the patients.
21 In other words, if you look at some of the
22 individual studies -- if you want we can pull
23 them out, but, you know, eight of ten
24 patients, nine of ten patients, all the
25 patients showed movement of the particles.

1 And then on top of that, you
2 have the review articles that talk about
3 migration of particles in the female
4 reproductive tract and are describing it as
5 an event that is known to occur. So it's
6 those things weighed together.

7 But certainly routine could be
8 supported by the observations where the
9 majority of the patients in the studies were
10 showing movement of inert particles.

11 Q. Is it your opinion that every
12 perineal application of cosmetic talc powder
13 results in talc being deposited on the
14 ovaries?

15 A. I have not formed that opinion,
16 no.

17 Q. Have you formed an opinion as
18 to with what frequency -- so let's say
19 someone uses a cosmetic talc on a perineal
20 application ten times. Out of those ten
21 times, have you formed an opinion as to how
22 many of those instances would talc deposit on
23 the ovaries?

24 MS. PARFITT: Objection.

25 THE WITNESS: I haven't formed

1 an opinion in that particular way, no.
2 I think what I've -- I've tried to
3 describe to you in my report is that I
4 believe it is known that inert
5 particles have the ability to migrate.
6 And based on that, I form the opinion
7 that it's my opinion to a reasonable
8 degree of scientific certainty, which
9 would be a more likely than not
10 standard, that particles of talc would
11 be migrating when women are using them
12 perineally. But I haven't told you
13 that it has to be a specific number,
14 no.

15 QUESTIONS BY MS. BRANSCOME:

16 Q. Have you done any analysis to
17 establish over a lifetime use of cosmetic
18 talc where the app -- the perineal
19 application, with what frequency during a
20 lifetime the talc may have been deposited on
21 that individual's ovaries?

22 A. So I certainly looked for
23 information to allow me to assess that, but
24 unfortunately those kinds of studies would be
25 unethical to do. Because that would be a

1 matter of sampling women during -- using them
2 and then taking biopsies, and that's
3 something that would be difficult to do. I
4 would say impossible to get approval to do
5 under human testing guidelines.

6 Q. Okay. So it's your opinion
7 that it is possible for talc that is applied
8 through a perineal application to reach the
9 ovaries, but you cannot say with what
10 frequency that occurs?

11 MS. PARFITT: Objection. Form.
12 Misstates her testimony.

13 THE WITNESS: That's not --
14 what I'm telling you is, I think it --
15 that to a reasonable degree of
16 scientific certainty that it migrates,
17 and that would be the standard of more
18 likely than not. I think it's more
19 likely than not that the talc is
20 reaching the ovaries when people are
21 using it perineally.

22 I did form the opinion -- and
23 I've talked about this at trial and
24 yesterday. I have formed the opinion
25 that this is a issue of chronic or --

1 or use of the products. In other
2 words, people aren't just using it
3 once, but people are using it -- you
4 can use the word "routinely," as a
5 habit, in their daily life perineally.
6 And that would be consistent with the
7 studies that have been done that have
8 looked at the issue of dose response.

9 And I discuss that in my
10 report, too.

11 QUESTIONS BY MS. BRANSCOME:

12 Q. Okay. But you have not made an
13 attempt to quantify, nor have you seen it in
14 the literature, the overall dose of talc that
15 someone might be exposed to in terms of
16 contact with the ovaries throughout their
17 lifetime, chronic use of cosmetic talc?

18 MS. PARFITT: Objection. Form.

19 THE WITNESS: Those -- that's
20 the kinds of studies that have not
21 been done and I believe could not be
22 done based upon ethics of human
23 testing. But certainly I -- that --
24 that data is not available that I'm
25 aware of.

1 MS. BRANSCOME: Okay. Can we
2 just go off the record for a second?

3 VIDEOGRAPHER: We are going off
4 the record at 12:23 p.m.

5 (Off the record at 12:23 p.m.)

6 VIDEOGRAPHER: We are back on
7 the record at 12:24 p.m.

8 QUESTIONS BY MS. BRANSCOME:

9 Q. As you sit here today, how
10 would you characterize the biological
11 mechanism by which you claim Johnson's baby
12 powder, their other cosmetic talc products,
13 present a risk of ovarian cancer?

14 A. So I outline this for you in
15 the MDL report. I think I have a section
16 on -- let's see if I can -- you want me to
17 tell you where or...

18 So paragraph 65, I think I set
19 out part of this argument or part of this.
20 And then also in paragraph -- I believe in
21 67.

22 Q. All right. Well, let me take a
23 step back.

24 Is it your opinion that the
25 biological mechanism by which talc, cosmetic

1 talc, can in your view cause ovarian cancer,
2 is that something that has been definitively
3 established?

4 A. What do you mean by
5 definitively? I mean, I think -- I believe
6 more likely than not that -- so I believe I
7 have reached a conclusion that I think what
8 the most likely biologically plausible
9 mechanism, but maybe you're ask -- meaning
10 something else.

11 Q. Okay. Well, let's start with
12 specifically you discuss a number of
13 different potential mechanisms in your
14 report. So if you believe you have reached
15 an opinion more likely than not about the
16 specific biological mechanism by which
17 cosmetic talc and specifically Johnson &
18 Johnson's products can cause ovarian cancer,
19 can you describe that for me?

20 A. So it's a chronic inflammatory
21 process, and so -- but like all compounds,
22 constituents, even drugs that we look at, we
23 don't know each individual step within the
24 molecular mechanism.

25 Instead, what we know is that

1 there are certain components to the process
2 of cancer that are consistent with the
3 effects produced by talc, and we know that
4 talc can produce a chronic inflammatory
5 process.

6 And so that's why I was
7 pointing you to the paragraph 65 and I think
8 67.

9 Q. Is it your opinion that
10 consensus has been reached in the scientific
11 community that cosmetic talc can cause
12 ovarian cancer through a chronic inflammatory
13 response?

14 MS. PARFITT: Objection.

15 THE WITNESS: I don't know that
16 that's exactly the opinion I've
17 formed.

18 Would you like me to -- I could
19 restate what I believe, but I don't
20 think that's exactly how I would state
21 it, no.

22 QUESTIONS BY MS. BRANSCOME:

23 Q. Okay. So then yes or no: Has
24 consensus been reached in the scientific
25 community that cosmetic talc can cause

1 ovarian cancer through a chronic inflammatory
2 process?

3 A. I don't believe I formed the
4 opinion either way, that it's yes or no,
5 because I haven't tried to -- I haven't tried
6 to form the opinion about what the -- in
7 other words, I haven't -- I can't say for
8 every scientist out there.

9 I certainly can tell you what I
10 believe based on what the consensus of
11 science says about mechanisms underlying
12 cancer and the consistency of those
13 mechanisms with talc, and then I have an
14 opinion about what I believe that information
15 says.

16 I do believe my opinions,
17 however, are consistent with some consensus
18 statements, such as the issue on the
19 mechanism is consistent with consensus
20 opinion reached by IARC, where they discuss
21 the inflammatory process as an underlying
22 biologically plausible mechanism that can
23 lead to ovarian cancer.

24 I think it's consistent with
25 the Canadian risk assessment where they

1 discuss those issues.

2 I think it's consistent with --
3 I don't know if the ACOG statement goes that
4 far on mechanism, but it does talk about
5 ovarian cancer. That's a recent statement.

6 And I believe it's consistent
7 with some of the -- I believe my opinions are
8 consistent with some of the opinions reached
9 by others in science, but that's the only way
10 I can answer that for you.

11 Q. Okay. Because you have not,
12 one way or the other, done an evaluation of
13 whether or not chronic inflammatory process
14 is a biological mechanism on which the
15 scientific community has reached general
16 consensus with respect to the causation of
17 ovarian cancer; is that correct?

18 MR. MEADOWS: Objection.

19 THE WITNESS: I can't tell you
20 that -- I can't tell you that every
21 body that's looked at it, but I have
22 tried to point you to evidence that I
23 believe is consistent with that.

24 For example, the IARC would be
25 a good example of consensus on

1 biologic mechanism because they have a
2 whole part of their assessment of
3 non-asbestiform talc and perineal
4 cancer -- of perineal use and ovarian
5 cancer that discusses mechanism. And
6 that is consistent with what I have
7 said. So there is a consensus
8 opinion.

9 But I guess what I'm saying to
10 you is I can't tell you that all --
11 all people who have put statements
12 have come to that exact opinion. But
13 there aren't that many places out
14 there that are addressing that issue
15 as far as the consensus on a
16 mechanism. There's more statements
17 about the relationship between ovarian
18 cancer and talc use than there are
19 drilling down to what the mechanism
20 must be.

21 QUESTIONS BY MS. BRANSCOME:

22 Q. Okay.

23 A. So that's the issue. It's a
24 little -- it's a little hard to answer that
25 yes or no because of that.

1 Q. Okay. When we talk about the
2 idea of biologic -- a biologically plausible
3 mechanism, what is your understanding of the
4 term "plausible" in that expression?

5 A. When I use the word
6 "biologically plausible mechanism" or
7 "biologic plausibility," I'm using it
8 consistent with what Bradford Hill uses,
9 that's it's the idea that the evidence that
10 available makes -- the evidence that
11 available supports a pathway where you can go
12 to exposure to response.

13 So in other words, there's a --
14 the biological information is consistent with
15 how we know cancer can develop. That's the
16 response we're looking at. And the exposure
17 we're looking at is known to produce those
18 kind of biologic events.

19 So as a result, based upon
20 knowing that there's a consistency between
21 the data that we have on the -- on the
22 exposure and the data that we have on the way
23 cancer can occur, those things -- those
24 things align. So that makes it biologically
25 plausible that that could occur.

1 Q. But you would agree that
2 biological plausibility suggests that it is a
3 plausible explanation, but it may not have
4 been established as the definitive pathway by
5 which a disease is caused, correct?

6 MS. PARFITT: Objection. Form.

7 THE WITNESS: Well, I would
8 agree that in the discussion of
9 biologic plausibility in the Bradford
10 Hill paper that is true. But if you
11 look at people's discussion of the use
12 of -- I want to say "biological
13 mechanism" rather than the word
14 "biologic plausibility," because
15 really as a toxicologist I'm trying to
16 understand whether there's a biologic
17 mechanism that makes sense. Those are
18 words I like to use. Does it make
19 sense that this exposure could lead to
20 this response.

21 And that involved looking at
22 the mechanistic data or the data on
23 the way toxic responses are produced
24 by talc, and whether or not they align
25 with the types of toxic insults that

1 are known to be able to produce,
2 specifically, ovarian cancer.

3 QUESTIONS BY MS. BRANSCOME:

4 Q. Is it your opinion that IARC,
5 for example, has concluded that the
6 biological mechanism by which talc may cause
7 ovarian cancer is chronic inflammation?

8 MS. PARFITT: Objection.

9 THE WITNESS: I don't know that
10 they have used -- they've described it
11 quite that way, but they do describe
12 what they believe is the biologically
13 plausible mechanism. Because they do
14 organize and use within the
15 definitions of how they describe some
16 things that are consistent with what
17 Bradford Hill uses.

18 QUESTIONS BY MS. BRANSCOME:

19 Q. Okay. And obviously you're
20 familiar with the IARC evaluation of talc
21 with respect to the possibility of causing
22 ovarian cancer, correct?

23 A. Yeah. If you mean the recent
24 one, yes, the most recent assessment.

25 Q. Yes.

1 And that IARC has in fact
2 classified cosmetic talc not containing
3 asbestos as possibly carcinogenic to humans,
4 correct?

5 A. It's a possible human
6 carcinogen 2B, that's correct.

7 Q. Okay. And if a product is
8 listed in the 2B category, does that
9 necessarily mean the product, in your view,
10 is carcinogenic?

11 A. Not always, because that comes
12 down to an assessment of -- then you're
13 putting together a -- a risk assessment that
14 looks at -- looks at -- across the
15 information that you have available. And
16 that may be that -- that the -- the possible
17 is all you can say, or it may be that you
18 believe that the information -- there's
19 enough information there to take it further.

20 Has a possibility -- that's
21 what I said, they do a hazard assessment.
22 They rank things on hazard based on -- on
23 unlikely -- not enough evidence, less -- the
24 possibility, the probability or it's known.

25 Q. In your opinion, is your

1 characterization of the risk of Johnson's
2 baby powder or talcum powder products with
3 respect to ovarian cancer, are you in the MDL
4 characterizing that risk as a higher level of
5 risk than what IARC characterized it, or do
6 you agree with the 2B characterization of
7 possibly carcinogenic?

8 MS. PARFITT: Objection. Form.

9 THE WITNESS: So I'm not IARC,
10 so I don't try to second-guess there.
11 They have reached a conclusion, and I
12 use that as part of my weight of the
13 evidence. So I haven't formed the
14 opinion they're right or wrong.

15 But I have done a different
16 assessment. My assessment, first off,
17 includes more information than IARC
18 had, so as a result, I have formed the
19 conclusion that I believe that it's
20 more likely than not that exposure
21 to -- perineal exposure to talc body
22 powders increases the risk of ovarian
23 cancer in women who use that product.

24 And I will put the caveat this
25 has to be chronic use or repeated use,

1 because I've gone -- I've said that
2 many times.

3 So that -- that is my opinion.
4 So that's a different statement and a
5 different assessment than what IARC
6 does.

7 But -- so I don't disagree with
8 their possible -- I weigh that, but I
9 believe the evidence for the risk
10 assessment shows me that it's more
11 likely than not that this -- this
12 exposure will increase the risk above
13 a background risk for women who are
14 using this product.

15 QUESTIONS BY MS. BRANSCOME:

16 Q. And how do you define chronic
17 or repeated use?

18 A. Well, that is variable within
19 the literature. For me, chronic is
20 exposure -- if as a toxicologist, I would
21 typically say chronic use is years of use.
22 It doesn't have to be daily, but it would be
23 years. That's the most common description
24 you see in toxicology, so I would say that's
25 fair. That's a fair assessment of my

1 opinion.

2 Q. Is there a threshold of the use
3 of Johnson & Johnson's talcum powder products
4 below which there is no increased risk, in
5 your opinion, of ovarian cancer?

6 A. We have not identified that
7 threshold. That's what's missing within
8 the -- the literature that exists today. So
9 I can't tell you whether or not with only a
10 thousand applications over a lifetime that
11 is -- is not enough for every individual or
12 not, but certainly I do believe that the --
13 that the exposure has to be habit, routine,
14 chronic, something that is done maybe not on
15 a daily basis but on a routine basis in a
16 woman's life.

17 So that is consistent, I think,
18 with the literature.

19 MS. BRANSCOME: Okay. We can
20 go off the record.

21 VIDEOGRAPHER: We are going off
22 the record at 12:36 p.m.
23 (Off the record at 12:36 p.m.)

24 VIDEOGRAPHER: We are back on
25 the record at 1:35 p.m.

1 QUESTIONS BY MS. BRANSCOME:

2 Q. Good afternoon again,
3 Dr. Plunkett.

4 A. Good afternoon.

5 Q. I want to talk a little bit
6 about the Health Canada assessment.

7 We talked about this before,
8 but this is something that you reviewed after
9 you completed your report which has been
10 marked as Exhibit 4, correct?

11 A. Yes, and I wanted to tell you,
12 I did not bring all those documents printed.
13 I apologize. So there is a separate Health
14 Canada draft risk assessment that I didn't
15 print.

16 Q. Okay. So when you're referring
17 to the Health Canada analysis, what document
18 are you specifically referring to?

19 A. So I'm referring to the -- the
20 combined documents, but there are times when
21 you've asked me questions that I've been
22 referring -- and I tried to say, I believe,
23 Taher.

24 But, yes, some of the questions
25 you asked me when I said Health Canada, I was

1 talking about the combined documents, which
2 would include their -- I guess it's called a
3 draft risk assessment document, yeah, which
4 refers to this document but is a separate --
5 is their own separate statement.

6 Q. As you sit here today, what is
7 your understanding of the current position
8 that has been articulated in the collection
9 of documents that you refer to as Health
10 Canada with respect to any potential
11 relationship between cosmetic talc and
12 ovarian cancer?

13 A. So that's why I did print out
14 the small one, because I think it summarized
15 it. So here, if you look at this Exhibit 6,
16 it makes specific conclusions or draws --
17 makes statements. And essentially it talks
18 about talc being a possible risk of ovarian
19 cancer, but then it gives women specific
20 advice about what to do in order to minimize
21 exposure to the products, and some of that
22 was relevant as well.

23 Just one reason I printed it
24 out, it has to do with either choosing an
25 alternative product or avoiding genital

1 exposure to talc.

2 And let me see the exact words
3 that they use, but --

4 Q. Before you do that, do you
5 agree with the characterization that cosmetic
6 talc presents a possible risk of ovarian
7 cancer?

8 A. No, I don't think that's my
9 opinion. I think my opinion is stronger than
10 that.

11 But are you talking about my
12 causation analysis opinion or just my risk
13 assessment opinion?

14 Q. I'm asking about any opinion
15 you intend to offer in the MDL.

16 A. Okay. So I will not be giving
17 the causation analysis opinion, so that -- I
18 will take that off the table.

19 So I think my opinion is a
20 little stronger because I say that the
21 exposure to the perineal -- the talc by
22 perineal application in women increases the
23 risk. So I'm not saying it's a possible
24 risk. I'm actually -- I believe that it
25 increases the risk. And I do believe that

1 there is a association between those two
2 things, the exposure and the response, which
3 is more than a possible association, if you
4 want to use those words.

5 But my assessment that I've
6 done is not exactly the same, for example, as
7 IARC does, which is more of just a hazard
8 assessment.

9 Q. Right.

10 So I'm focusing my questions
11 now on your risk assessment as compared to
12 the documents that you've supplied us with
13 with respect to Health Canada. And if I
14 understand it correctly, are you stating that
15 your opinion with respect to the relationship
16 between cosmetic talc and ovarian cancer, you
17 believe that it is an association that is
18 stronger than a possible risk; is that
19 correct?

20 A. Well, I don't say it's a
21 possible risk; I say there is an increased
22 risk. So I think it's a different statement,
23 yes, absolutely.

24 Of course, I'm not Health
25 Canada, so, you know, they have a framework

1 upon which they make decisions, and I'm doing
2 an analysis based on what I have done. And
3 so it's not exactly the same, although some
4 of the same documents and information is
5 weighed within -- and then that's when you
6 have the issue of what Health Canada does
7 versus what they rely upon.

8 But this Taher risk assessment
9 is just one piece of information that Health
10 Canada has weighed in their assessment if you
11 read their -- their draft risk assessment.

12 Q. So the question I have about
13 the Taher risk assessment, earlier you were
14 referring to the fact that you have only seen
15 a quantitative assessment of the weight of
16 particular components of scientific evidence
17 in evaluating epidemiological studies; is
18 that correct?

19 A. So that's what I typically see,
20 yes. And I don't know that -- I've never
21 seen it. But the typical approach would be
22 to use it there as opposed to using it in the
23 context of a human health risk assessment
24 based on animal in vitro data.

25 Q. All right. Are you familiar

1 with something called the Klimisch scoring
2 system?

3 A. I don't know if I am now.
4 You'll need to show me what it is you're
5 referring to. The name doesn't ring a bell,
6 no.

7 Q. Okay. So it's not something
8 that you've used in the past?

9 A. No, not that I recall using.

10 Q. All right.

11 A. Unless it has another name, and
12 that's why I'm asking you.

13 Q. All right. So if you have
14 actually -- it's the document in front of you
15 that we've already marked as Deposition
16 Exhibit 5, I believe.

17 A. Yes.

18 Q. And that is the Taher study
19 that we were discussing and is cited by the
20 Health Canada risk assessment.

21 If you turn to page 5 -- well,
22 actually beginning on page 4, do you see
23 there is a section entitled "Literature
24 Search and Identification of Relevant
25 Nonhuman Studies"?

1 Do you see that?

2 A. Yes.

3 Q. And this is related to an
4 analysis that these authors performed on
5 potentially relevant animal and in vitro
6 studies, correct?

7 A. Yes, that is true.

8 Q. All right. And it states here
9 that "all retrieved studies were examined for
10 relevance, reliability and overall quality
11 using the Klimisch scoring system."

12 Do you see that?

13 A. Yes, I do see that. So I have
14 seen that before. I just didn't -- I didn't
15 recall it.

16 Q. Okay. And so would you agree
17 that it is possible and in fact has been done
18 in a study that you rely on to apply a
19 quantitative scoring system to animal and in
20 vitro studies, particularly in the context of
21 looking at the relationship between talc and
22 ovarian cancer?

23 A. Well, I didn't say it was
24 impossible. I said I don't believe it's
25 routine based on my experience.

1 So, yes, if they stated they've
2 done -- we'd have to pull the supplementary
3 materials out, but I recall them doing
4 scoring based on epi studies but not on
5 the -- all of the animal studies that they
6 talk about. But we can pull it out and look.
7 I could be wrong.

8 Q. Okay. Did you review the
9 supplementary material 7, 8 and 9?

10 A. Yes, I did, and we'd have to
11 pull them out because I don't recall the
12 details.

13 Q. All right. We may take a look
14 at those in a minute.

15 It talks about them classifying
16 the animal and in vitro studies into four
17 categories of reliability.

18 Do you see that?

19 A. Yes.

20 Q. So did you make any attempt,
21 when you were reviewing the various studies
22 in reaching your opinion about the potential
23 risk of talc in causing ovarian cancer, did
24 you make any attempt to separate out the
25 different pieces of evidence into categories

1 of reliability like the authors of this paper
2 have done?

3 A. I didn't do it exactly the way
4 they did it, but I certainly do do that as
5 part of my screening.

6 I told you one of the
7 characteristics or one of the assessments I
8 make is whether I believe the data is
9 reliable data that I can -- that I can use in
10 a weight of the evidence. So I make a -- and
11 when I talk about reliability, I'm talking
12 then about things such as I mentioned, peer
13 review, whether or not there is statistical
14 analysis, whether or not the study is
15 designed in a way that's consistent with
16 general principles of toxicology, control
17 groups or not control groups.

18 Those kinds of things I do -- I
19 do consider when I am assessing the use of a
20 study or not.

21 Q. Is it your testimony here today
22 that contained within your report that's
23 marked as Exhibit 4, I could find
24 categorization of reliability of each of the
25 pieces of scientific literature that you have

1 included in your weight of the evidence
2 analysis? Is that your testimony today?

3 A. No, that's not what I'm telling
4 you, no.

5 Q. Okay. So you would agree that
6 you did not -- first of all, did you develop
7 categories of reliability in which you
8 separated the particular scientific studies
9 into as part of your weight of the evidence
10 analysis?

11 A. I do look at -- I do categorize
12 studies based upon my assessment of their
13 reliability and their ability to be used to
14 answer the question I'm asking, but I -- I
15 already told you, I didn't do it the way it's
16 set out here. I didn't have these specific
17 five categories, no. That's not what I did.

18 Q. Okay. Other than the CIR 2013
19 publication, which you have said that you do
20 not find reliable and you assign little
21 weight to it, can you point me to another
22 place in Exhibit 4 where you assign a
23 specific category of weight that you have
24 given to a particular study that you include
25 in your weight of the evidence analysis?

1 A. If what you're asking me is do
2 I make a specific statement next to each
3 study that I discuss about little weight or
4 great weight, no, I don't do that, if that's
5 what you're asking me.

6 Q. Okay. As part of the
7 collection of documents that relate to Health
8 Canada that was provided to us as part of
9 your new reliance list, did you review a
10 document entitled weight of the evidence --
11 or "Weight of evidence: General principles
12 and current applications of Health Canada"?

13 A. Yes, I've seen that.
14 (Plunkett Exhibit 8 marked for
15 identification.)

16 QUESTIONS BY MS. BRANSCOME:

17 Q. All right. We will mark this
18 as Plunkett Deposition Exhibit Number 8.

19 All right. The document that I
20 just handed you that's marked as Plunkett
21 Deposition Exhibit Number 8, are you familiar
22 with that document, Dr. Plunkett?

23 A. Yep, I've seen this before.

24 Q. Is this listed among the new
25 materials that have been added to your

1 reliance list?

2 A. I believe it was, yes.

3 Q. Okay. And so for this one I
4 just want to direct your attention to the
5 conclusion section -- well, let me ask you
6 first: How does this document relate to the
7 collection of documents with respect to
8 Health Canada that you identified as relevant
9 to your opinion?

10 A. It was one of the materials
11 that they rely upon or they cite. That's the
12 reason I pulled it. It was -- I pulled
13 documents that they provided on the website
14 that were cited.

15 Q. Okay. And if you could turn to
16 page 11 of that document, there's a
17 conclusion section. The first sentence of
18 the third paragraph reads, "The given --
19 given the context-specific nature of each
20 risk assessment and the diversity of tools
21 and criteria applicable, transparent
22 documentation of the specific application of
23 the WOE approach is especially important."

24 Did I read that correctly?

25 A. Yes, you did.

1 Q. And is your understanding of
2 WOE that it is weight of evidence?

3 A. Yes, that's correct.

4 Q. Do you agree with this
5 statement?

6 A. In a regulatory context, I do
7 believe that that is true, because within the
8 regulatory context when they do the risk
9 assessment, there's a need to understand why
10 decisions are made. So, absolutely, in a
11 regulatory context, I would agree that this
12 kind of transparency is even being adopted by
13 EPA.

14 Q. And is it your opinion then
15 that a different level of transparency is
16 needed for expert testimony in court?

17 A. No, that's not what I'm saying.
18 I'm saying that's a different process. And
19 that's what part of this process is. It's
20 understanding the ability to provide a dialog
21 about what was done.

22 So as a result, this is
23 something that is common to the work that
24 I've done in the past. Even in a
25 nonlitigation context with my regulatory

1 clients, doing a risk assessment doesn't
2 necessarily involve the same level of detail
3 that a regulatory -- a regulator would apply
4 to the transparency of the assessment. Not
5 to say that it couldn't be done, but it's
6 just -- I would say it's not necessarily
7 typical.

8 Q. So this specifically refers to
9 transparent documentation.

10 Do you see that?

11 A. Yes.

12 Q. Would you agree that the report
13 that you have produced in the MDL does not
14 have documentation of the specific
15 application of the weight of evidence
16 approach?

17 MS. PARFITT: Objection.

18 Excuse me, objection. Form.

19 THE WITNESS: I disagree to an
20 extent because I did attempt to
21 provide in my report a description of
22 the methods that I used and the
23 resources that I've relied upon for a
24 discussion of how those methods are
25 used.

1 And then in addition to that,
2 I've attempted to lay out for you in
3 my report a discussion of the pieces
4 of evidence that I've relied upon,
5 including some -- for some of those --
6 that's one of the reasons I got so
7 detailed in the section on migration
8 and providing you an analysis of each
9 of the papers that I relied upon and
10 what I thought was important within
11 them that led to my -- the formation
12 of my opinions.

13 So I disagree to some extent.

14 QUESTIONS BY MS. BRANSCOME:

15 Q. Okay. Turning back to what
16 Taher did in classifying different studies
17 into different categories of reliability.
18 Have you done that type of analysis in the
19 past where you have separated out different
20 studies into different categories of weight
21 or reliability as part of an overall
22 analysis?

23 A. Well, I do that every time I do
24 a weight of the evidence when I separate into
25 categories first based upon the type of

1 study. In other words, as I discussed many
2 times in deposition, when you're talking
3 about doing a human health risk assessment,
4 there's certain types of data that are most
5 relevant. I mean, when they use the word
6 "reliable" -- I don't know that many of these
7 studies have the same level of reliability as
8 far as peer review, but they're -- for
9 example, on the issue of migration, it's my
10 opinion that the data from the human studies
11 is a more reliable or relevant source of
12 information. And I've laid out why, because
13 of differences in the anatomy, things like
14 that, with the data.

15 Q. Are you familiar with the term
16 "binning exercise"?

17 A. Yes, I am. And that is
18 certainly something that I have used in other
19 aspects of work that I have done.

20 Q. Did you do a binning exercise
21 in rendering your opinions and what you've
22 provided to us in the context of your
23 opinions in the MDL?

24 A. Yes, that's the exercise I
25 start with. I'm binning them into human,

1 animal, mechanistic, in vitro data. That's
2 the first bins.

3 In fact, in the copper work we
4 did, that's what we did. We separated the
5 data into in vitro/only mechanistic
6 information, animal studies, did we have
7 human studies.

8 And we also looked at
9 studies -- we had a separate bin of exposures
10 like I do. I have studies that just address
11 the issue of exposure potentially.

12 So, yes, it's -- it's
13 consistent with doing that. It's --
14 essentially binning is just separating the
15 information into groups based on what
16 questions those -- those data can answer.

17 Q. Okay. Have you ever -- do you
18 ever separate them into bins based on the
19 level of weight that you would give a
20 particular study?

21 A. I do that when I'm analyzing
22 each of the studies within that group or that
23 bin. That's what I do. I give them -- in my
24 weight -- in my analysis, I weigh those
25 studies based upon my judgment on the

1 relevance, the reliability, the power of the
2 study, the statistical analysis that's done,
3 the inclusion in animal studies, in
4 particular, of controls. Those are all parts
5 of that analysis that I do. So, yes, I do do
6 that.

7 And then in -- there have been
8 exercises that I've done in the past with
9 other individuals where we may have taken a
10 yellow sticky note and put down on top of it
11 animal data with exposure information, animal
12 data without exposure information. That's
13 the process that I'm doing when I am looking
14 across the data. I'm separating those pieces
15 of data into groups and what types of
16 questions they can answer.

17 So that is consistent with what
18 I do when I do a weight of analysis approach
19 in the work that I do in both nonlitigation
20 and litigation context.

21 Q. Okay. But we have no specific
22 documentation of the different ratings that
23 you gave the various pieces of evidence that
24 you included in your weight of the evidence
25 analysis, aside from occasional references to

1 giving something less or more weight,
2 correct?

3 A. Well, I certainly -- I told you
4 I have not given numerical values that you're
5 asking me, but I've attempted to do that when
6 I have described them in groups, when I talk
7 about human versus animal versus in vitro.
8 Because I've already told you, I believe,
9 it's my opinion that certain types of
10 information are more informative than others.
11 And so the more informative it is, the more
12 weight you're giving it in -- obviously in
13 your analysis.

14 But it is a different exercise
15 than what is described here. And here I'm
16 pointing to Exhibit 8. And it's a different
17 exercise, obviously, than what a regulatory
18 body is required to do where they are trying
19 to come up with ways to increase the
20 transparency when no one can go and actually
21 talk to each of the regulators individually
22 to understand what their thinking was.

23 Q. Okay. Returning to biological
24 mechanism for a minute, why doesn't
25 inflammation generally, including chronic

1 inflammation, cause ovarian cancer?

2 A. Because it doesn't change the
3 phenotype of the cell. It has to -- the --
4 and I discuss that. You have to -- you have
5 to set up a chronic inflammatory process that
6 leads to changes within the cellular
7 phenotype to go from a cell that is -- that
8 is -- is dividing normally to a cell that
9 isn't.

10 So it's -- it's the same issue
11 that you address even in a study in animals.
12 Why do not all animals exposed to -- exposed
13 to a chemical develop tumors. It's the idea
14 that something has to be initiated beyond the
15 exposure or maybe beyond inflammation to lead
16 to the series of events.

17 And so, yes, it's recognized
18 that you can get inflammation, and
19 inflammation can go down the road in becoming
20 a carcinogenic process, or inflammation can
21 no longer -- can stay where it is. It
22 doesn't progress beyond just a chronic
23 inflammatory process.

24 Q. And so if you had a study that
25 demonstrated that a particular agent causes

1 inflammation, you would need more information
2 in order to make the conclusion that that
3 agent can in fact cause cancer, correct?

4 MR. MEADOWS: Objection.

5 THE WITNESS: You would look
6 for more informative information,
7 exactly, which is why, when I've
8 talked about the individual
9 constituents in the context of
10 consistency on mechanism for cancer,
11 I've pointed to documents where that
12 information has been discussed.

13 So like when I talk about
14 asbestos or cobalt or I point to
15 the -- for example, the IARC
16 assessment where they go through
17 that -- that discussion of the fact
18 that there's not just data showing
19 that a biologically plausible
20 mechanism may be inflammation, but
21 there's also data to show that that
22 can lead to tumor development as well.

23 QUESTIONS BY MS. BRANSCOME:

24 Q. Okay. How does talc change the
25 phenotype of the ovarian cell?

1 A. So this is one of the details
2 we don't know, other than generally it's
3 changing the phenotype to go from a normal
4 cell to a tumor cell. That is being
5 observed. When you find the presence of the
6 tumor, that is what you're observing.

7 Q. Does pure talc with no other
8 constituent components, can it change the
9 phenotype of an ovarian cell?

10 MR. MEADOWS: Objection.

11 THE WITNESS: So that's a
12 difficult question to answer with
13 certainty because of the fact that I
14 don't believe that we have assurance
15 that any of the studies are done with
16 essentially pure talc.

17 However, in the studies that
18 claim to have been done with pure
19 talc -- for example, the NTP study
20 claims to have been done with pure
21 talc. So if that is pure talc, truly
22 is, then that study is an example of
23 evidence for the chronic inflammatory
24 process leading to preneoplastic
25 lesions that are setting down the road

1 mechanism towards cancer.

2 So there are data out there.

3 The problem you have, I believe, in
4 the literature is whether or not,
5 based on the discussion that is
6 becoming apparent now with sensitivity
7 and ability to take the natural
8 product and actually determine exactly
9 what's in it, that I don't think there
10 is the ability to assure that any --
11 any of these studies with the samples
12 of talc they're using is absolutely,
13 100 percent, only platy talc. I think
14 there's -- there's some concern about
15 that. But certainly you will take --
16 you have to take what is discussed
17 within the study as evidence from what
18 they're claiming.

19 So many of the studies say we
20 used asbestos-free talc or platy --
21 pure platy talc and we got a toxic
22 response.

23 QUESTIONS BY MS. BRANSCOME:

24 Q. Would it be possible to design
25 an experiment -- and now I'm talking about an

1 in vitro or an animal experiment -- by which
2 you would expose either cells or animal to
3 talc with different constituent products to
4 identify or separate out the individual
5 effects of the components? Is that a study
6 that you could design as a toxicologist?

7 A. I think that would be difficult
8 to do, but I'm not saying impossible to do.
9 And here's the -- there are some very
10 specific considerations you'd have to put
11 into that design.

12 I would argue that some of that
13 is already available, where we have studies
14 that have looked at the dose-response effects
15 for toxicity with cobalt, with chromium, with
16 asbestos.

17 When you get to asbestos and
18 talc, it's more problematic because then the
19 question is what is -- what is it? What are
20 the specific characteristics in all the
21 different studies of exactly what the
22 asbestos was versus exactly what the talc
23 was.

24 But I think you could attempt
25 to do that, and then the question would be,

1 being able to use that data not so much to --
2 not so much to identify a dose response for a
3 certain insult, but to look at the fact --
4 look at potency differences across the
5 compounds. And then there's the issue of
6 then looking at additivity when you know you
7 have a complex mixture.

8 So that could be done, but,
9 again, it would be difficult to do based on
10 what we know about talc, being able to really
11 know that -- you would have to really be very
12 careful that what it is that you're looking
13 at is -- is not containing any of those
14 things that we unfortunately know co-occur
15 with constituents within the natural product.

16 But no one has done those
17 studies. I point that out. I haven't seen
18 that study that you're asking for. I have
19 not seen somebody do that.

20 Q. And a study like that would be
21 relevant in evaluating the potency of the
22 individual constituents and what might
23 actually be the driving factor for phenotypic
24 change, correct?

25 A. Not necessarily. I would argue

1 that we already have an answer to that by
2 looking at the data that's been collected on
3 the complex mixture itself. So the issue
4 would be why -- the question is what do you
5 gain by being able to say that we're only
6 pointing to this constituent or that
7 constituent. That isn't what is occurring.

8 What people are exposed to is
9 the complex mixture, not just each one of
10 those individual components. To me this is
11 not a case of asbestos-only exposure. This
12 is a case of exposure to consumer products
13 that are talc that may have within them at
14 any given time -- and data indicates that
15 there are substantial chance that asbestos
16 may be in -- is in certain of these products.

17 But my opinions are not
18 dependent on there being asbestos there at a
19 particular level or copper there -- or, I'm
20 sorry, cobalt there at a particular level
21 because my opinions are based on the
22 observations we have on the complex product
23 as it exists.

24 Q. And you recognize that
25 different types of talc and different talc

1 products have different constituent
2 components in different amounts, correct?

3 A. Some can. I agree with that.
4 That is true.

5 So if you're being broad, as in
6 pharmaceutical-grade versus industrial-grade
7 or chemical-grade, yeah, because they'll have
8 a purity level assigned.

9 But as far as what the -- what
10 the components are, it isn't always defined
11 even specifically within that.

12 Q. Okay. And does the presence of
13 oxidative stress in a tissue indicate that
14 cancer will develop in that tissue?

15 A. Will definitively develop?
16 Not -- I don't think you could say
17 definitively develop, but it's certainly in
18 the biologically plausible mechanism that's
19 been understood to lead to chronic
20 inflammation and also has been linked to
21 cancer.

22 So that's the issue of not
23 necessarily saying it has to be there, but it
24 certainly is something that is observed
25 routinely in cases where carcinogenesis has

1 been linked to an inflammatory response.

2 Oxidative stress is often a triggering

3 mechanism.

4 Q. Does the body have protective

5 mechanisms that limit tissue damage from

6 oxidative stress?

7 A. Yes, which is why not everybody

8 that's exposed to any particular chemical is

9 going to get cancer. Some people will

10 respond better. Some cells will respond

11 better. Some individuals in a population at

12 one time in their life may respond better.

13 Q. You would agree that in vitro

14 studies do not account for the body's natural

15 defenses outside of what exists at the

16 cellular level, correct?

17 A. Depends on the in vitro study

18 that's being done and whether or not there is

19 components added.

20 So I've seen studies done where

21 they take cells and then add extra levels of

22 glutathione to try to protect the cells from

23 certain stressors that could lead to damage,

24 but I agree with you that an isolated cell on

25 its own is a different microenvironment than

1 an intact tissue, which is a different
2 environment than an intact animal, which is
3 even different than an intact human being.
4 Yes, they're all -- you look at those levels
5 of evidence or those types of evidence
6 differently, depending upon the end points
7 you're collecting.

8 Q. And so you would give lower
9 weight to an in vitro study as compared to an
10 in vivo study, for example?

11 A. Depends on the question you're
12 asking. I would give a lot of weight if the
13 question is what do I know -- if I want to
14 try to understand the biologically plausible
15 mechanism, some of those in vitro studies are
16 some of the most important, because it's the
17 only ones that allow us to answer a question.

18 If the question is higher level
19 about what is the evidence to show that
20 there's an increased risk overall for cancer
21 or a hazard for cancer, then certainly you
22 need to have more than an in vitro study.

23 So as -- so on -- if you want
24 to layer it up, obviously, if all you had was
25 in vitro data, you'd have much less

1 confidence in the conclusions you can draw
2 unless you had some in vivo data. In vivo
3 data is going to allow you to interpret the
4 in vitro data.

5 So certainly there would be
6 more weight given in that assessment to the
7 fact that you had in vivo data.

8 Q. And so when you made the
9 statement that, for instance, you always give
10 more weight to human data, is that true, or
11 does that also depend?

12 A. Well, it depends on whether you
13 have human data. So if I have human data and
14 I have a doubt, any doubts at all, about
15 whether or not the exposure-response
16 relationship would be affected by the way the
17 animal studies are designed, then, yes, I
18 would give more weight to the human studies.

19 In a case, however, such as
20 inhalation exposure assessments where
21 there -- it's much better, actually, to do an
22 animal study where we can do a dose response
23 across different sizes of particles and
24 actually observe lesions as they develop over
25 time, which is why I love -- I love the NTP

1 93 study of interim sacrifices, looking at
2 that issue. That data is very reliable in
3 order to understand the risk of lung damage
4 as compared to a human study where we don't
5 have those serial time points, doses that are
6 defined tightly.

7 So -- and the relevance between
8 those kinds of initial lung injury in certain
9 animals versus humans match fairly well.

10 That's my problem, though, in
11 the case with the perineal exposure. I'm
12 saying to you, because of the route of
13 contact -- we need to be able to get it there
14 to the tissue -- the human data is extremely
15 important.

16 Q. So is it fair to say that in
17 some circumstances animal data gets more
18 weight than human data and in other
19 circumstances human data gets more weight
20 than animal data? It is circumstance
21 dependent?

22 A. I would put it a different way.
23 I would say in some cases animal data is
24 weighted in a similar manner to human data.
25 I don't necessarily say it would get more

1 weight, but it could if you only had one
2 crappy human study, one really badly designed
3 human study, and I had a GLP quality cancer
4 bioassay then, absolutely. I mean, IARC does
5 this. They look at that animal data and say,
6 "This one tells us -- answers the questions
7 we want to answer, and this very poorly
8 designed case series isn't going to allow us
9 to do that."

10 So you could, but I would say
11 it's more the other issue, that you look at
12 animal and human more on an equal basis if
13 the relevance and the extrapolation can be
14 done reliably.

15 And that's the question you
16 have to ask, can I extrapolate from animals
17 to humans in a reliable manner.

18 Q. Okay. Would you agree that the
19 response to cosmetic talc can vary depending
20 on tissue type in the body?

21 A. Yes, I would say that that is
22 true, whether or not there's certain
23 protective barriers in place, for example,
24 yes.

25 Q. And so in order to draw

1 conclusions based on a study of one cell
2 type's reaction to cosmetic talc to another,
3 you would need to understand the differences
4 in similarities between those two cell types,
5 correct?

6 MS. PARFITT: Objection.

7 THE WITNESS: It's a different
8 question. So you were asking me
9 about -- I didn't think you were just
10 asking about cells. I thought you
11 were asking me about like routes of
12 exposure, dermal versus inhalation.
13 Those things differ.

14 Cell types may or may not.
15 That may or may not be true. Because
16 if two cells -- two different cell
17 types in the body share similar
18 characteristics as far as the -- for
19 example, if they're both epithelial
20 cells or mesothelial cells, those type
21 of cells you would expect to respond
22 the same way.

23 But I would agree that, for
24 example, a neuronal cell versus a GI
25 cell versus a liver cell, there could

1 be differences in how they would
2 respond, yes, and so you would -- you
3 would look at those things
4 individually.

5 QUESTIONS BY MS. BRANSCOME:

6 Q. And so it's important to
7 understand the differences and the
8 similarities between the different cell types
9 before drawing conclusions using studies from
10 different cell types?

11 MS. PARFITT: Objection.

12 MR. MEADOWS: Objection.

13 THE WITNESS: I certainly think
14 you should consider the cell types
15 that are being used and whether or not
16 those cell types are ones that are
17 relevant to your risk assessment
18 question you're asking, yes.

19 QUESTIONS BY MS. BRANSCOME:

20 Q. Okay. You would agree as a
21 toxicologist, dose is an important part of a
22 toxicological analysis of an agent, correct?

23 A. If you're doing risk, yes. If
24 you're only doing hazard, it may not be as
25 important. It depends upon the question

1 you're asking about hazard.

2 Do you want me to explain?

3 Q. I do want you to explain the
4 difference between a risk analysis and a
5 hazard analysis.

6 A. Okay. So in an initial hazard
7 analysis, if the question is, is there a
8 hazard associated with exposure, let's say,
9 by inhalation, it may not matter whether it
10 was a high dose or a low dose study. Both of
11 those can identify hazard.

12 Then you ask the question: Is
13 there a dose-response relationship? That's
14 the next step beyond hazard.

15 So hazard is -- to me is
16 identifying the end points that you're going
17 to monitor for toxicity, sort of the target
18 organs, those things, and so whether or not
19 there's a dose-response study available, it
20 wouldn't be as important.

21 But certainly when you go to
22 that next step to assess risk, you'd like to
23 be able to see whether or not there is a
24 dose-response relationship in the effect that
25 you're assessing.

1 Q. Okay. And in your -- in your
2 report, as part of your risk assessment that
3 you did in the MDL -- this is paragraph 12 on
4 page 8.

5 A. Yes, I'm there.

6 Q. Okay. You state about
7 two-thirds of the way down the paragraph that
8 "weight of the evidence methods were critical
9 to defining the literature that identified
10 the hazards of talc exposure as well as
11 defining the dose-response relationship
12 between talc exposure and the risk of adverse
13 health effects."

14 Did I read that correctly?

15 A. You did. That's correct.

16 Q. All right. Is it your view
17 that in the case you have reached an opinion
18 that defines the dose-response relationship
19 between talc exposure and the risk of ovarian
20 cancer?

21 A. It depends what you mean by
22 define. I can tell you what I mean in this
23 sentence, and maybe that would help you.

24 Q. Dr. Plunkett, it is your
25 report. And so I am asking you, using your

1 own definition of "define," have you rendered
2 an opinion that defines the dose-response
3 relationship between talc exposure and the
4 risk of ovarian cancer?

5 A. I have formed opinions about
6 the dose-response relationship generally, but
7 unfortunately -- I answered that question for
8 you earlier when you asked me, I think, about
9 is there -- I don't know if you used the word
10 "threshold," but I did.

11 So the available information
12 doesn't allow us to identify an ultimate
13 threshold, for example, in the case of women
14 exposed to talc perineally and their -- and
15 their development of ovarian cancer.

16 Instead, in defining the dose
17 response, what we can do with the data -- and
18 that is what I attempted to do. This is
19 where you look at defining the dose response
20 in the animal studies, which we can look at,
21 or defining dose response in cell studies,
22 showing that as the dose increases, the
23 hazard and the risk increase. So risk
24 actually you quantify. There's a certain
25 response at this dose and a different

1 response at the next dose, or have we
2 plateaued, that the responses are the same as
3 dose increases.

4 So that, I did do that as part
5 of my assessment, trying to define the dose
6 as far as how that linked to the responses in
7 each of the studies I looked at.

8 Q. You would agree, though, that
9 some studies did not show a dose relationship
10 between talc and ovarian cancer or the
11 clinical signs that were indicative of the
12 potential for development into ovarian
13 cancer, correct?

14 MS. PARFITT: Objection.

15 THE WITNESS: If you're talking
16 about the human data; is that what
17 you're referring to? Or are you
18 talking about all -- any of the data?

19 QUESTIONS BY MS. BRANSCOME:

20 Q. Any of the data.

21 A. So I would disagree on the
22 animal data. I think on the animal data they
23 often -- most of the animal studies I've
24 relied upon have looked at more than one dose
25 or at least looked a no exposure versus a

1 dose, and most of them have looked at more
2 than one dose.

3 In the case of the human
4 studies, unfortunately, some of those studies
5 were not designed to be able to define dose.
6 In other words, the questions weren't asked,
7 for example, of the individuals even in the
8 prospective studies. Some of those
9 included -- did not include the information
10 collected on frequency and duration of use.

11 So if it's not collected,
12 obviously, I don't have it to look at. And
13 that's one of the limitations of human
14 epidemiological investigations, is that it
15 often is not designed appropriately to look
16 at dose response.

17 Q. Is it your opinion that there
18 are no studies looking at talc and the risk
19 of ovarian cancer in which the authors of the
20 study have concluded there was no clear
21 pattern of increased risk with dose?

22 MS. PARFITT: Objection.

23 THE WITNESS: No, that's not
24 what I've said. No. It's very
25 possible that an individual paper

1 or -- that they may make a -- an
2 author may make a statement, but I'm
3 talking about looking -- this is
4 weight of the evidence. I'm looking
5 across. And I'm saying, across the
6 data, when I look at the human data
7 versus the animal data, for example,
8 versus in vitro studies, the in vitro
9 studies and the animal studies allow
10 you to look at dose response for talc
11 toxicity.

12 The -- even the animal studies
13 allow you to look at dose response for
14 development of precancerous lesions,
15 you're on the way to cancer, for
16 example, in the NTP studies.

17 And then in the human studies,
18 some of those studies are designed
19 such that the authors could draw
20 conclusions about dose response and
21 some are not.

22 Even in some of the studies
23 where they attempted to look at dose
24 response, some of the authors indicate
25 they don't see an effect. So that is

1 true. And part of that may be driven
2 by the design of the study, the number
3 of individuals in the study, the way
4 that the questions were asked.

5 There's limitations on the way that
6 information is collected.

7 If you want to look at each
8 study, we can, but --

9 QUESTIONS BY MS. BRANSCOME:

10 Q. So my question to you, whether
11 you agree or disagree with the author's
12 conclusion, is simply that if you look at the
13 overall animal and human studies that you
14 cite in your report or have considered on
15 your reliance list that look at a potential
16 dose-response relationship for talc toxicity,
17 do some of those studies conclude that there
18 is not a dose-response relationship?

19 MS. PARFITT: Objection.

20 THE WITNESS: I disagree for
21 talc toxicity, but I would say if
22 you're going to limit it to the issue
23 of the ovarian cancer response, I
24 would agree. I have seen that in some
25 of the studies.

1 I think talc toxicity, I don't
2 know if anybody has made the
3 comment -- I would doubt it -- that
4 there is no dose response for toxic
5 effects of talc.

6 QUESTIONS BY MS. BRANSCOME:

7 Q. Okay. You discuss in your
8 report -- wait a moment. It's in
9 paragraph 58 on page 38. And I just want to
10 make sure I understood what you were citing
11 here.

12 In paragraph 58 you state that
13 "It is important to remember that
14 administration of even a single dose of talc
15 in animals has been shown to produce adverse
16 effects locally at the site of the exposure."

17 What are you referring to
18 there?

19 A. Acute doses. In other words,
20 in studies that have described installation
21 of a single dose of talc in some form into a
22 tissue, that they are observing adverse
23 responses.

24 An example of that may be
25 the -- I think it's Hamilton. Is that the

1 one where they stilled it into the ovaries
2 with a single dose?

3 Q. So these are large-dose
4 exposures?

5 A. Well, not all --

6 Q. Or are they, I should say?

7 A. I don't know that they all are,
8 no. There are -- there are -- I don't think
9 I have attempted to quantify large in this
10 sentence.

11 What I'm stating here is not an
12 issue of large versus small. It's an issue
13 of the fact that there are toxic effects with
14 single exposures. And I'm just making the
15 comment -- this has to do with hazard, right?
16 It's the idea even a single dose -- or a
17 single exposure you can get irritant,
18 inflammatory reactions at the site of
19 exposure. And that's all I'm trying to say.
20 That's why I'm citing as reviewed by EPA. I
21 believe EPA even makes a very similar
22 statement.

23 Q. Okay. Do you take into
24 account -- there are some studies for
25 which -- at least my reading of your report

1 is that you give them less weight because you
2 believe that the individuals who conducted
3 the study had been paid by either a company
4 or agencies that had some investment in the
5 outcome of the study; is that correct?

6 A. Is that my opinion?

7 Q. Yes.

8 A. For any particular study,
9 you'll need to show me what you're pointing
10 to. I do have opinions about some of the
11 work by Drs. Huncharek and Muscat, yes. I
12 think I address that specifically, and that
13 has -- that's not so much to do with my
14 weight of the evidence; that has more to do
15 with transparency and what was being
16 disseminated to the public and disseminated
17 to the FDA as far as evaluations.

18 That's a different issue than
19 the weight of -- the weight of -- the weight
20 of the evidence assessment for risk. I think
21 those were separate.

22 Q. So then I'll ask you that.

23 In doing your weight of the
24 evidence analysis for risk, have you
25 discounted the weight that you've given to

1 any particular piece of scientific evidence
2 based off of potential affiliations of the
3 authors?

4 A. I certainly did with the CIR
5 review document. I've already told you that.
6 And that's because I have evidence that shows
7 it's not just an affiliation issue, but it's
8 actually -- it's more -- it's more important
9 than that.

10 Q. Are there any other examples?

11 A. I think that's the only one
12 right now as I sit here that I can tell you
13 that I had identified as carrying little
14 weight because of an issue of either
15 authorship or input in the way it was
16 described.

17 There are certainly studies
18 within my weight of the evidence evaluation,
19 some of which were performed by industry. I
20 certainly look at that issue, but unless I
21 have -- have a reason to believe that there's
22 an inherent bias based on something I know,
23 they go into the weight of the evidence
24 without making a correction for that.

25 In many cases that I work in

1 litigation, I will find situations like the
2 situation here with Huncharek and Muscat
3 where I have, for example -- I think this
4 came up in the Risperdal litigation for me.
5 It's the idea that there was a series of
6 papers put out by an individual investigator
7 where documents that I could get access to
8 show me that indeed their analysis was not
9 done by them but it was ghostwritten by
10 somebody else. So that gives me pause,
11 although I would never have known that unless
12 I had access to internal documents.

13 So initial weight of the
14 evidence I did not discount it, but then I
15 went back and had to reevaluate the role
16 those studies played in my overall
17 assessment.

18 Q. Do you take into account in any
19 way in evaluating the weight of a study if it
20 is conducted by someone who serves as an
21 expert on behalf of the plaintiffs in the
22 active litigation?

23 A. It would be the same -- same
24 issue. I certainly consider it as part of
25 what I look at, but just like if they were an

1 expert for the defense versus an expert for
2 the plaintiff, you judge that information
3 based on what you know. And if I don't have
4 information to discount it, I will not
5 discount it.

6 But absolutely, I understand.
7 Just as people we all -- look at some of the
8 things I've published where I have said my
9 work was sponsored by the American Chemistry
10 Council. You know, people -- that's why you
11 disclose the conflicts. You put it there so
12 people can weigh it if they want, but it
13 doesn't mean you discount the work
14 automatically.

15 And so I think for any paper,
16 plaintiff, defense, whoever it is that's
17 writing it, you need to consider it based on
18 the information you have. And if you believe
19 that you have information to indicate that
20 there's some issue with the reliability of
21 the analysis, then absolutely you consider
22 that.

23 Q. So, for example, when you rely
24 on Dr. Longo's characterization of the
25 constituent components in samples that he has

1 tested, that he reports are Johnson's baby
2 powder, did you also consider the work that
3 was done by experts that have been retained
4 on behalf of the defendants to characterize
5 the components of Johnson's baby powder? Do
6 you give them equal weight?

7 A. So I haven't seen a variety of
8 the documents that you're talking about,
9 so -- because I have not worked in the
10 litigation cases that have involved asbestos
11 only. So -- which I think is where those
12 documents are.

13 In the litigation I -- in the
14 litigation I worked in, I am aware of what
15 other experts on both sides have said. I
16 don't believe I've seen an analysis from a
17 defense expert that is -- that is like
18 Dr. Longo's, at least in the litigation I've
19 worked in. Certainly I would consider that
20 and look at that if it's available, and I
21 would consider it.

22 I would point out, Dr. Longo's
23 analysis is not the piece of evidence that
24 you start with, though. You start with what
25 I discuss in the published literature first,

1 because there are published documents out
2 there in the literature that describe exactly
3 what Dr. Longo is now describing.

4 Q. What published documents are
5 those?

6 A. Those are Dr. Blount's reports
7 in 1991, which is before the litigation came
8 about, is my understanding.

9 There's also -- there's five or
10 six. I can tell you the paragraph.

11 Q. For Johnson's baby powder, I
12 would be interested in that, yes.

13 A. So I -- I'll have to look and
14 see if it's Johnson's baby powder only, but
15 certainly there is other evidence on the
16 issue of asbestos contamination and
17 specifically in talc.

18 So I -- you want me to find the
19 paragraph for you?

20 Q. Please. If you think there is
21 published literature documenting asbestos in
22 Johnson's baby powder, I would like to see
23 that.

24 A. So this is my paragraph 32.
25 And I'd have to pull each of these articles

1 out because I don't recall what each of them
2 says. But I'm pointing to Paoletti, Blount,
3 Mattenklott, Moon, Gordon, Anderson, Rohl,
4 Pooley and Rowlands, Blejer and Arlon,
5 Cralley, Millman.

6 And then I cite -- and then of
7 course the next piece of evidence is there
8 are actually documents from J&J and Imerys
9 that show detection of asbestos or
10 asbestos-like minerals in talc.

11 Q. As you sit here today, can you
12 identify which of these published articles
13 that you list in paragraph 32 relate to
14 Johnson's baby powder?

15 A. I would have to pull them to
16 answer that.

17 Q. Okay.

18 A. As I sit here, I'd have to pull
19 them. But I would refer you -- I know at
20 least some of them do based on the statement
21 I've made, but...

22 Q. So you did not make an attempt
23 in this paper to identify which products were
24 being analyzed in these specific articles.
25 It's not indicated on the face of this

1 paragraph, correct?

2 A. I don't tell you on the face,
3 but you if read the sentence I said, "When
4 commercially available, talcum powder
5 products were analyzed, including powders
6 sold by Johnson & Johnson. The data has
7 shown that the powders contained varied
8 levels" -- and I'm saying "fibers," so it's
9 just asbestos -- "including fibers that
10 stated to be asbestos."

11 So to tell you which of those,
12 I'd have to pull them. And I apologize, I
13 didn't bring them all with me.

14 Q. Have you been provided --
15 you're aware that Dr. Blount's paper does not
16 identify Johnson's baby powder in the face of
17 the article, correct?

18 A. I believe that's true. You'd
19 have to go to her deposition, I believe,
20 where she's given -- where she discusses what
21 the source of that was, and maybe even a --
22 there may even be a separate document,
23 actually, not a deposition, that was -- that
24 was in the files of Johnson & Johnson that
25 goes along with that, but I'd have to go

1 look.

2 Q. Have you reviewed Dr. Blount's
3 deposition?

4 A. I have reviewed a -- something
5 by Dr. Blount. Whether it was trial
6 testimony or deposition, I have seen
7 something, yes, that she has said regarding
8 this issue.

9 Q. To the extent that there is
10 confusion about whether or not a sample
11 tested by Dr. Blount is in fact Johnson's
12 baby powder, would you reduce the weight that
13 you give that particular piece of evidence in
14 evaluating whether asbestos has been present
15 in Johnson's baby powder?

16 MS. PARFITT: Objection. Form.

17 MR. MEADOWS: Objection.

18 THE WITNESS: I don't know
19 reduce the weight because -- because
20 there's -- there are plenty of
21 documents here that talk about that.

22 I would consider it --
23 certainly it would -- it's not so much
24 weight. It's a different bin. We'll
25 call it a bin, a different bin of

1 information. There's information on
2 talc powders generally, and then
3 there's some information that's
4 specific to certain body powders.

5 So certainly -- would I pay
6 attention if they identified it? Yes.

7 But in the statement I'm making
8 here, I'm not claiming that every one
9 of these is relating to just the
10 powder sold by Johnson & Johnson.
11 This is across the available
12 information that's public and then
13 also the information that's available
14 in the files of Johnson & Johnson.

15 QUESTIONS BY MS. BRANSCOME:

16 Q. What is your definition of
17 asbestos?

18 A. My definition of asbestos is
19 exactly what the different documents describe
20 it typically. It's a fibrous mineral,
21 typically. It occurs in a variety of
22 different forms. Most of the times they'll
23 say "asbestos." Sometimes they'll say
24 "chrysotile." Sometimes they'll say
25 "tremolite." Sometimes they'll say

1 "anthophyllite." Those are the three most
2 common ones I see. But those are all mineral
3 forms of asbestos.

4 So just like IARC puts those
5 all within one bin, I'm putting those all in
6 one bin because they have a similar toxicity
7 profile.

8 Q. Is it your view that each of
9 the different types of asbestos has the same
10 toxicity profile?

11 A. They all have the same ability
12 to cause cancer, but they have different
13 potencies. So they do have -- there will be
14 some differences in the dose response and the
15 potency of them, but certainly they've all
16 been linked as being carcinogens by IARC.

17 And I would agree, when you
18 look at their data, there is data and
19 evidence to indicate that.

20 Q. Which type of asbestos is the
21 most potent?

22 A. For which end point? For lung
23 cancer? I believe chrysotile is. For other
24 end points, I'd have to go look. I mean,
25 chrysotile is the sharp -- is the sharp --

1 the sharded-type structure.

2 But there's data on fibrous --
3 the fiber -- the fibrous forms of asbestos
4 rather than the -- or the amphibole forms of
5 asbestos as opposed to chrysotile, which is
6 the serpentine form.

7 Q. Do you consider yourself an
8 expert in asbestos?

9 A. Not in --

10 MS. PARFITT: Objection.

11 THE WITNESS: Not the geology
12 of asbestos, no.

13 I have expertise in toxicology
14 as it relates to interpretation of the
15 data related to asbestos. I have
16 never give -- given testimony in a
17 case on asbestos, but it's something
18 I've studied in the past in my work as
19 a toxicologist, not as a testifying
20 expert.

21 QUESTIONS BY MS. BRANSCOME:

22 Q. What role does your analysis of
23 the possibility that there may be asbestos in
24 Johnson's talcum powder products play in your
25 risk assessment in the MDL?

1 A. Has to do with the fact that we
2 have a complex mixture that has multiple
3 carcinogenic substances.

4 And asbestos is important from
5 the aspect of the way that it has been
6 assessed even by regulatory bodies, the idea
7 that even very low levels of fibers pose a
8 cancer hazard and a cancer risk in
9 individuals have been shown to be
10 carcinogenic.

11 So that's what I'm saying about
12 potency of asbestos is different than potency
13 of some other carcinogens that you might look
14 at. But the importance of it is it's a
15 complex mixture, talc, body powders, a
16 complex mixture that includes constituents
17 that are known human carcinogens as well as
18 some that are -- been ranked other ways by
19 regulatory bodies.

20 Q. If Johnson's talcum powder
21 products do not contain asbestos, does that
22 change your opinion with respect to the risk
23 they pose with respect to ovarian cancer?

24 A. No, and I think that was very
25 clear if you looked at my first report. So

1 even -- there's -- I don't think in any of my
2 reports I've opined that without looking at
3 the complex mixture that we wouldn't be here.

4 In other words, I have not
5 opined that if it doesn't have -- if it
6 doesn't have asbestos, it's not a risk. I
7 have not opined that, and I don't believe
8 that, because I think there is independent
9 risk for the fact that we have a complex
10 mixture of talc that has been tested and
11 shown to be carcinogenic.

12 It's my opinion, I told you --
13 maybe it wasn't you. I may have told this
14 yesterday, I'm sorry, to Mr. Smith that I
15 believe that there is evidence to show that
16 there is a significant exposure to asbestos
17 based on the data that's been collected.

18 But certainly, you know, in
19 some -- the data has shown that in the assays
20 that have been done or the analyses that have
21 been done that you can't say that talc is
22 asbestos-free.

23 Q. Well, so --

24 A. So --

25 Q. -- the question I have

1 specifically relates to ovarian cancer.

2 Is it your view that through an
3 exposure route that is relevant for ovarian
4 cancer, that the use of Johnson's talcum
5 products involve a substantial exposure to
6 asbestos?

7 A. I believe based on the use of
8 the products that -- where the data has been
9 collected that there would be a substantial
10 exposure to asbestos, regardless of how
11 you're exposed, perineal -- perineally or by
12 inhalation.

13 Q. What is your basis for reaching
14 that conclusion?

15 A. It's looking at the number of
16 fibers that have been detected in the
17 products, in looking at the -- the widespread
18 nature of the presence of asbestos fiber --
19 asbestos in the talcum powder products and
20 the fact that even though it's at a very low
21 level by their -- their level of detection,
22 again, can't be said to be asbestos-free.

23 So regardless of whether it's
24 talc that's being applied perineally or a
25 talc that you're inhaling while you're

1 applying it perineally, the fibers are still
2 going to be present within that talc.

3 Q. Have you or anyone done an
4 analysis of the dose of asbestos to which
5 someone might be exposed perineally?

6 A. I haven't done a specific
7 calculation, no.

8 Q. Has anyone done that
9 calculation?

10 MS. PARFITT: Objection. Form.

11 QUESTIONS BY MS. BRANSCOME:

12 Q. That you have seen?

13 MS. PARFITT: Objection.

14 THE WITNESS: I'm trying to
15 remember whether I saw that done in
16 any of the documents related to
17 Dr. Longo.

18 I don't know. I'd have to go
19 look.

20 QUESTIONS BY MS. BRANSCOME:

21 Q. Okay. So as you sit here
22 today, can you give an opinion to a
23 scientific degree of certainty, reasonable
24 degree of scientific certainty, that an
25 individual would be exposed to a dose of

1 asbestos above background through the
2 perineal use of Johnson's talcum powder
3 products?

4 MR. MEADOWS: Objection.

5 MS. PARFITT: Objection.

6 THE WITNESS: I don't think
7 that's the opinion I have formed to
8 date, but certainly the opinion I have
9 formed is that the data I have seen
10 indicates that you can't separate out
11 talc without asbestos versus talc with
12 asbestos in the information that's
13 been collected. Because there's --
14 all -- the information that's been
15 collected has shown there's no
16 evidence that asbestos-free talc is
17 available.

18 If by asking that question
19 you're trying to say that it's the
20 asbestos alone that's causing the
21 cancer, that is not my opinion. So
22 that is when the dose issue would
23 become very important for asbestos.

24 QUESTIONS BY MS. BRANSCOME:

25 Q. Okay.

1 A. So that's -- so that's a
2 different question I have not answered.

3 Q. And in reaching your opinion
4 that there is no evidence that asbestos-free
5 talc exists, you have not been provided with
6 the reports by the defense experts, including
7 Dr. Matthew Sanchez, analyzing Johnson's
8 talcum powder products for the presence or
9 absence of asbestos, correct?

10 MS. PARFITT: Objection. Form.

11 I think you're aware that the
12 MDL expert reports have not yet been
13 provided to us.

14 MS. BRANSCOME: Yeah.

15 MS. PARFITT: I'm just making a
16 point.

17 THE WITNESS: I have not seen a
18 report by Dr. Sanchez. I assume I
19 will, because typically after -- later
20 in the litigation, once all experts
21 have been deposed or revealed, I'm
22 usually given defense expert reports
23 and their deposition testimony. So I
24 expect to see that; I just haven't
25 seen it yet.

1 QUESTIONS BY MS. BRANSCOME:

2 Q. And you haven't seen it in any
3 of the cases in which you've rendered an
4 opinion, correct, not just the MDL?

5 A. Well, none of the cases that I
6 have worked in have involved the issue of
7 looking for asbestos exposure.

8 The cases I have worked on have
9 been talking about talc exposure that may
10 include asbestos as a constituent, but it
11 wasn't focused on asbestos exposure.

12 So, no, none of the cases I
13 worked on have provided testimony in that
14 area.

15 You understand what I'm saying?

16 Q. Let me just make it clear. You
17 have not, in any of the cases in which you
18 have offered opinions with respect to the
19 contents of talc, been provided with an
20 expert report or testimony by Dr. Sanchez
21 about what he did or did not find in
22 Johnson's talcum powder products with respect
23 to asbestos?

24 MS. PARFITT: Objection. Form.

25 THE WITNESS: So I can't tell

1 you that I have not. I don't recall
2 it. That's all I can say. I don't
3 recall that name.

4 QUESTIONS BY MS. BRANSCOME:

5 Q. It's certainly not something
6 you discuss in your report, correct?

7 A. No, I do not. And I don't know
8 that it's in my reliance materials. That's
9 why I'd ask you to look there, because if
10 it's in my reliance materials, then I've seen
11 it.

12 Q. Okay.

13 A. And I mean big reliance
14 material list, not my reference list.

15 Q. All right. With respect to the
16 other potential constituents of talc, have
17 you done any analysis to provide an answer as
18 to how much -- what dose of chromium, for
19 example, an individual might be exposed to
20 through the perineal use of Johnson's talcum
21 powder products over a lifetime?

22 A. No, and I have -- well, I know
23 it's a separate deposition. We discussed
24 this yesterday. No, I have not done a -- a
25 calculation of a potential dose with perineal

1 application for any of the heavy metals. So
2 the three that I've mentioned, no, I have not
3 done that calculation.

4 Q. You would agree, based on your
5 training and experience as a toxicologist,
6 that in order for an agent -- and we can talk
7 specifically about a metal -- to present a
8 risk of cancer it needs to be bioaccessible,
9 correct?

10 A. If by bioaccessible you are not
11 limiting that definition to solubilized into
12 the blood and carried systematically, yes, I
13 would agree with that. Bioaccessible meaning
14 it has to be in a form that can somehow
15 interact with the tissue, yes, I agree with
16 that. But it could be as simple as tissue
17 contact versus needing to be solubilized.

18 Q. Okay. Is silica bioaccessible?

19 A. It depends on the form of the
20 silica. So silica particles can be
21 bioaccessible if inhaled and found on the
22 surface of the lung. That can cause injury
23 at the site of the lung. So that's an
24 accessibility to that particular tissue that
25 it contacts.

1 Q. We talked earlier -- it's
2 somewhat related to bioaccessibility, but we
3 talked about the way in which different
4 particles might move specifically through the
5 genital tract in women.

6 Do you recall that?

7 A. Yes. A general discussion.

8 Q. Yes.

9 And when you testified that
10 starch and talc might not move at the same
11 rate, do you have an opinion as to which
12 might move more quickly through the tract?

13 A. I haven't formed that opinion,
14 no.

15 Q. Okay. And do both talc and
16 starch particles remain in the body for the
17 same length of time?

18 A. I haven't done an analysis to
19 see if the data tells us what the -- what the
20 differences might be. I would expect there
21 to be differences, which is what I told you
22 earlier, because I would expect the starch to
23 be able to be solubilized, where I would not
24 necessarily expect the talc to act in that
25 same manner.

1 Q. Is cornstarch capable of
2 causing an inflammatory process?

3 A. It can. It is -- but it is --
4 it's a different level of risk for
5 inflammatory responses than is talc, just by
6 its chemical nature.

7 Q. Have you done an analysis in
8 your report that examines the differences
9 between the inflammatory response that can be
10 triggered by talc as opposed to cornstarch?

11 A. I haven't analyzed inflammatory
12 response. Instead, what I've done is done a
13 comparison of what the toxicity -- the
14 differences in the toxicity potential have
15 been described in medical literature, and I
16 cite -- I have a paragraph where I cite to
17 some sources that talk about the differences
18 in the toxicity potential or biocompatibility
19 of starch versus talc.

20 Q. Now, I had a question about
21 your supplemental report that was marked as
22 Exhibit 3 to the deposition.

23 At paragraph 67...

24 A. Okay.

25 Q. You identify here six heavy

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1 metals - arsenic, chromium, lead, cobalt,
2 cadmium and nickel - that in your
3 supplemental report dated August 29, 2018,
4 you say have been reported across lots of
5 talc powders.

6 Do you see that?

7 A. Are you in -- now you're in my
8 MDL report or here?

9 Q. No.

10 A. Oh, so where are you? I'm
11 sorry.

12 Q. Same report. It's the sentence
13 that begins at the bottom of page 6.

14 A. Okay. Hold on.

15 About that they have varied at
16 the levels --

17 Q. Yes. So you identify six
18 different types of heavy metals.

19 Do you see that there?

20 A. Yes, I do.

21 Q. Okay. And the question I had
22 for you was that in your report in the MDL,
23 if you look at paragraph 36 --

24 A. Yes.

25 Q. -- you identify -- you identify

1 only three heavy metals: chromium, cobalt
2 and nickel.

3 Do you see that?

4 A. Yes.

5 Q. Why did you remove three of the
6 heavy metals?

7 A. It's not so much removing.
8 Those three heavy metals that I focused on in
9 my MDL report are ones that have been talked
10 about with a similar mechanism of action as
11 far as irritation and biologic -- biologic
12 plausibility mechanism being irritation and
13 inflammation.

14 So that's why I focus on those
15 three, which may not -- which is not
16 necessarily the case for some of the others,
17 even though they're also -- have a
18 carcinogenic hazard, pose a risk.

19 Q. So in your -- as part of your
20 risk assessment that you performed in the
21 MDL, are you offering the opinion that to the
22 extent they exist in any of the Johnson
23 talcum powder products, that arsenic, lead --

24 A. Cadmium.

25 Q. -- and cadmium play any role in

1 the risk of developing ovarian cancer?

2 A. That is not an opinion that I
3 would be offering in the MDL.

4 Q. Okay. Now, you talk about
5 these heavy metals having been classified by
6 different agencies as either known probable
7 or possible human carcinogens, correct?

8 A. You're in my MDL report again?

9 Q. Oh, yes.

10 A. Okay. I'm sorry. Okay. Let
11 me get there.

12 Yeah, I do have that
13 discussion. I'm just trying to find it.

14 Q. Sure.

15 A. Okay. Yes, I'm there.

16 Q. Is it your view, based on your
17 expertise, that because a compound can cause
18 one type of cancer, it can cause all types of
19 cancer?

20 A. No, not necessarily. It
21 depends on the -- well, it depends on a
22 couple of things. It depends on what's been
23 studied. Have all types of cancer even been
24 studied. And then it also -- it also depends
25 upon, I believe, the route of exposure as

1 well. So can it get to where it could cause
2 that, could it distribute there. And then in
3 addition to that, what data has been
4 collected. Is there enough data, for
5 example, to show that there's extrapolation
6 from animals to humans in the types of tumors
7 or is it -- or if we have good human data,
8 then we would focus on the types of cancers
9 that you're seeing in humans, for example.

10 Q. Okay. But you recognize even
11 where there is complete data some compounds
12 can cause one type of cancer and they are
13 incapable of causing another type, correct?

14 MS. PARFITT: Objection. Form.

15 THE WITNESS: I don't know
16 about incapable, but I would agree
17 that you certainly would see -- you
18 could potentially see different
19 observations.

20 If you're talking about animals
21 versus humans, or are you talking
22 about --

23 QUESTIONS BY MS. BRANSCOME:

24 Q. If humans.

25 A. Based on what you had seen in

1 the animals; is that what you're asking me?

2 Q. Yes.

3 A. Yes. So, yes, there is not
4 always a one-to-one concordance. So that's
5 why -- that's why I made the comment that
6 it's important to have some human data or
7 experience, so that you can put in context
8 the data you collected in animals.

9 I would say to you there are
10 certain kinds of tumors in animals, for
11 example, that are shown to be not relevant at
12 all to human risk assessment. Like four
13 stomach tumors in rats is an example. I've
14 dealt with that one a lot.

15 Q. What types of cancer -- type or
16 types of cancer are the basis for the
17 classification of chromium as a known human
18 carcinogen by IARC?

19 A. So I have to pull it out, but I
20 believe that there may be some GI cancers and
21 maybe some skin cancers, but I'm not sure.
22 I've got it pull it out. It's been a while
23 since I've looked at it.

24 Q. Okay. Have you done an
25 analysis to evaluate whether or not the types

1 you can extrapolate with scientific basis
2 from one type of cancer cause to ovarian
3 cancer with respect to the heavy metals
4 specifically?

5 A. Well, I haven't attempted to
6 that, because I haven't attempted to define a
7 independent risk for each of those metals
8 individually.

9 The issue -- the issue I have
10 with those metals is -- there's a paragraph
11 here where I talk about pathogenesis of
12 carcinogenesis, where I talk about different
13 stages of cancer development and the fact
14 that inflammatory responses may be operating
15 at all those different stages.

16 So the issue is you have
17 potential -- you have compounds that are
18 known to produce cancer or have been shown to
19 have a potential risk of cancer. They share
20 a similar mechanism to talc, so as a result
21 of that, they factor into your risk
22 assessment as far as there being an exposure
23 to a mixture.

24 But on the issue of ovarian
25 cancer, I'm looking at the data that's been

1 collected on talc itself, which would be talc
2 with the constituents that could include the
3 metals. But certainly I'm not saying that it
4 is -- without the presence of one or the
5 other of these there would be no risk of
6 ovarian cancer. I'm not saying that either.

7 Q. So my question is, though, can
8 you point me either to scientific literature
9 directly documenting that these heavy metals
10 can cause ovarian cancer or to scientific
11 literature that enables you to extrapolate
12 from the types of cancer that they are known
13 or believed to cause to ovarian cancer?

14 A. So I -- on the issue of can I
15 point you to the data on ovarian cancer, I'd
16 have to go back. I can't answer that without
17 looking at the assessments.

18 But on the other -- second
19 question you asked me, that's the question I
20 was just trying to answer before. It's the
21 idea that regardless of where the cancer is
22 developing, the fact that these compounds
23 have the ability to stimulate similar toxic
24 responses in tissues could lead to a --
25 setting up a situation where the -- where the

1 tissue is primed for cancer development.

2 Q. And do you have --

3 A. And so that --

4 Q. Sorry.

5 A. And that has to do with the
6 basic science of carcinogenesis when you look
7 at underlying mechanisms, especially with
8 tissue contact, direct tissue contact, with
9 irritants or inflammatory processes.

10 But I would -- I am not -- I
11 have not formed the opinion, again, that with
12 or without either one of these that I would
13 expect ovarian cancer to be the target. I'm
14 saying that ovarian cancer risk is increased
15 based on exposure to talc, which includes a
16 variety of constituents.

17 Q. Okay. And do you cite anywhere
18 in your report to studies documenting -- I
19 know you said you'd need to go look at them,
20 but I'm asking if it's in your report
21 anywhere a discussion of any studies showing
22 that the particular heavy metals that you
23 cite as potential constituents of Johnson &
24 Johnson's products have been demonstrated to
25 increase a risk for ovarian cancer on their

1 own?

2 A. So, no, I haven't addressed
3 that in my report. And again, I think that's
4 inconsistent with the way I'm using these
5 data. But that's fine. I mean, no, I
6 haven't done a specific assessment of ovarian
7 cancer risk with each of those metals
8 individually.

9 Q. I would ask the same questions
10 for the different fragrance constituents that
11 you allege in your report are potential
12 carcinogens.

13 Have you done any analysis, and
14 can you point me to any scientific studies
15 that establish that those particular
16 compounds are capable of causing ovarian
17 cancer?

18 A. No, I haven't done that
19 analysis, but, again, general principles of
20 toxicology and cancer risk assessment, when
21 you look at the presence of multiple --
22 excuse me, multiple carcinogens with similar
23 mechanisms of action, you would assume in
24 your risk assessment that those risks could
25 be additive.

1 So, again, that's what I'm
2 pointing to and why I have cited the data.

3 Q. Now, you talked about -- when
4 we were discussing mechanism, you said that
5 inflammation alone is not necessarily
6 sufficient to cause cancer, correct?

7 A. Yes, I did.

8 Q. All right. Do you have
9 scientific studies that show that any of the
10 heavy metals or the fragrance constituents
11 that you identify as potential carcinogens
12 create -- generate phenotypic changes like
13 you discussed were next for the formation of
14 cancer?

15 A. I believe that data is
16 available on nickel. I need to go back and
17 look at chromium and cobalt, but I do believe
18 with nickel you'll find similar data on
19 tissue irritation and inflammatory processes.

20 Nickel is also a sensitizer, so
21 it has interaction with the immune system, so
22 I do believe that for nickel you can find
23 some of that data.

24 Q. Okay. But as you sit here
25 today, can you point me into any of that

1 that's discussed in your report?

2 A. No specific discussion other
3 than, again, all -- the IARC -- I'm citing to
4 the IARC assessments, and the IARC
5 assessments for each of those discuss
6 carcinogenesis and a biologically plausible
7 mechanism being linked to the ability of
8 these compounds to induce oxidative stress
9 and/or inflammatory processes.

10 Q. Okay. In your opinion, you
11 talk about the mixture of constituents that
12 are involved in talc.

13 Have you done any analysis to
14 look at how the different constituents
15 interact with each other?

16 A. Well, yes, that's my issue at
17 looking at underlying mechanism.

18 But are you asking me -- I
19 certainly don't have a -- the only studies
20 that I have to rely upon on the interaction
21 of the mixture is the actual studies on the
22 powders themselves, where we know that the
23 powders contain constituents other than just
24 platy talc.

25 Q. Okay. And do the constituents

1 need to have the same underlying potential
2 carcinogenic mechanism for them to have an
3 additive effect?

4 A. By general principles of
5 toxicology, yes, you look at mode -- mode of
6 action or mechanism of action before you
7 apply that additivity principle to the cancer
8 risk assessment.

9 Q. And so as you sit here, you
10 believe there have been scientific
11 documentation that nickel might operate
12 through the same biological mechanism as you
13 purport talc to operate, but you're not sure
14 about the other heavy metals or the fragrance
15 constituents; is that correct?

16 MS. PARFITT: Objection.

17 THE WITNESS: For the fragrance
18 constituents, I'd definitely have to
19 pull because I haven't looked at that
20 individual assessment in a while.

21 For these three, what I do know
22 is that they do share the ability to
23 at least induce oxidative stress.

24 What I can't recall for
25 chromium and for cobalt is whether

1 they're taking it the next step from
2 oxidative stress to inflammatory
3 process. I believe that they do, but
4 I'd have to check, whereas I know
5 nickel has been shown to lead to an
6 inflammatory process after oxidative
7 stress has been induced.

8 QUESTIONS BY MS. BRANSCOME:

9 Q. And you would agree, even more
10 than requiring an inflammatory process, you
11 would actually have to see that these
12 compounds can generate phenotypic changes,
13 correct?

14 MS. PARFITT: Objection.

15 THE WITNESS: Well, we know
16 they do because they've been shown to
17 be carcinogenic. If you've been shown
18 to be carcinogenic, you've done a
19 phenotypic change in the cell from a
20 normal cell to a cancer cell.

21 So we know they have the
22 capability to induce tumors, or
23 cancer, all three of those, at least
24 in animals if not in humans as well,
25 because two of them are known human.

1 So those two -- we'd have human data
2 to show that.

3 But on the issue of cobalt, it
4 may only be -- I need to go back and
5 look, but it may indeed just be animal
6 data.

7 QUESTIONS BY MS. BRANSCOME:

8 Q. And so your basis for that
9 would be the IARC classification?

10 Is that where I would go to
11 look if I wanted to look at it after this
12 deposition?

13 A. I'd go to the IARC reviews.
14 I'd go to those three which I believe I have
15 cited down here for you and given you where
16 to go to find them.

17 Q. Okay. You discuss in your
18 report -- and if you'd like to reference it,
19 it's paragraph 69 on page 47 -- the concept
20 of genotoxic and nongenotoxic carcinogens.

21 Do you recall that?

22 A. Yes.

23 Q. And as you sit here today, is
24 it your opinion that talc is more likely a
25 nongenotoxic carcinogen?

1 A. As the direct insult, yes. And
2 I would like to -- I would like to point out
3 that in the literature -- the reason I have
4 this paragraph here is because in the
5 literature in the past, in the area of
6 chemicals, it's been -- toxicologists have
7 attempted to put two bins, direct genotoxic
8 insult versus nondirect genotoxic. It
9 doesn't mean you can't get a genotoxic event
10 after the initiation.

11 So I want to make sure you
12 understand that. I'm not saying that there
13 is no possibility of this chemical in its --
14 in its process of inducing cancer leading to
15 indirect genotoxicity, but I'm talking about
16 the direct mechanism at the site of the cell.

17 So talc, for example, has been
18 shown to not be genotoxic in cells. And so
19 that's why I believe, then, when I look at
20 the rest of the data that fits, that it fits
21 the definition of a nongenotoxic carcinogen
22 by its initial mechanisms to induce cancer.

23 Q. Okay. And if talc is, in fact,
24 a nongenotoxic carcinogen, it would suggest
25 that there is likely a threshold dose below

1 which it does not have a carcinogenic effect,
2 correct?

3 MS. PARFITT: Objection.

4 THE WITNESS: It is possible,
5 and that's the problem. In order to
6 fully assess that, you would have to
7 have the data to prove it.

8 But that's the assumption. You
9 assume with nongenotoxic carcinogens
10 that you could identify a level where
11 you wouldn't turn on that indirect
12 mechanism. So that -- yes, that is
13 true.

14 QUESTIONS BY MS. BRANSCOME:

15 Q. And you have not been able to
16 identify, nor can you point to, scientific
17 literature that identifies a threshold -- a
18 threshold dose for talc with respect to its
19 carcinogenic potential for ovarian cancer,
20 correct?

21 A. Not a specific dose, but I
22 think that's why I mentioned to you -- and
23 I -- I think that's why Canada, when you look
24 at their document, they talk about
25 discouraging routine use generally. So it's

1 the issue of what -- single use of a body
2 powder or an occasional use is a different
3 risk assessment than routine use.

4 So if you want to talk about
5 thresholds that way, that's very imprecise,
6 but you could do that. You can talk about
7 whether or not there -- I do believe there's
8 a different risk profile for one or two uses
9 of talc body powder versus a risk profile of
10 somebody who uses it routinely, because I
11 think that fits that threshold definition.
12 It's the idea that you have limited
13 availability for enough particles to migrate
14 to lead to the tissue toxicity that it cannot
15 be recovered from or repair.

16 Q. You're familiar with the
17 concept of the precautionary principle,
18 correct?

19 A. Yes.

20 Q. All right. And you understand
21 that Health Canada may have made
22 recommendations with respect to product usage
23 that are purely precautionary, correct?

24 MS. PARFITT: Objection. Form.

25 THE WITNESS: I disagree that's

1 what they've done, but is it possible
2 that they would do it? Any regulatory
3 agency, it's possible they could do
4 it, yes.

5 QUESTIONS BY MS. BRANSCOME:

6 Q. Do you have any information
7 with respect to Health Canada's
8 decision-making, other than what you have
9 read on the face of the documents?

10 A. That is all I have to look at
11 is what is provided on the website.

12 Q. Okay. And so the statement
13 that you think Health Canada was suggesting a
14 dose threshold by their statement of
15 discouraging routine use, you're basing that
16 entirely on what you read on the piece of
17 paper, correct?

18 MS. PARFITT: Objection. Form.

19 THE WITNESS: Well, that's what
20 they state. So, yes, I'm -- I am
21 telling you what I see on their
22 website. If that's what you're asking
23 me, yes, that is true.

24 QUESTIONS BY MS. BRANSCOME:

25 Q. Okay. Can you point me --

1 well, do you discuss -- have you looked at,
2 as part of your opinion specifically in the
3 MDL, the studies exploring a potential link
4 between asbestos and ovarian cancer? Just
5 asbestos.

6 A. Some of the studies, yes, but I
7 have not -- I have not done a separate risk
8 assessment just for asbestos by itself,
9 because I have not assumed that there is
10 asbestos-only exposure.

11 Does that make sense?

12 But I do cite -- for example, I
13 cite to some of the early literature on -- so
14 this -- I guess where this opinion comes in
15 is on hazard and warning. So in the warnings
16 I talk about when it was known that asbestos
17 was linked with cancer, because the warning
18 standard is not causation proven but the
19 identification of the potential. And so that
20 is in my report on warnings, but that is not
21 within my discussion of the weight of the
22 evidence for risk assessment of the talc
23 product.

24 Q. Okay.

25 A. Does that make sense?

1 Q. Uh-huh.

2 For example, have you rendered
3 an opinion about what dose of asbestos
4 exposure would be necessary to cause ovarian
5 cancer in an individual?

6 A. No, I have not formed that
7 opinion at this time.

8 Q. Okay. Do you have an opinion
9 about the background level of asbestos to
10 which individuals are exposed with no
11 increased risk of any type of cancer?

12 A. No, I do not have an opinion.
13 I do believe others do, but I do not.

14 Q. Okay. You may have been asked
15 some of these questions before, but I will
16 keep them brief.

17 Have you ever published any
18 articles that state that talc causes ovarian
19 cancer?

20 A. No, I have not.

21 Q. Have you ever publicly
22 expressed the opinion that talc increases the
23 risk of ovarian cancer outside of literature?

24 A. No. My work has been in the --
25 in the courtroom.

1 MS. BRANSCOME: I think we can
2 take a break.

3 VIDEOGRAPHER: We are going off
4 the record at 2:57 p.m.

5 (Off the record at 2:57 p.m.)

6 VIDEOGRAPHER: We are back on
7 the record at 3:13 p.m.

8 MS. BRANSCOME: Dr. Plunkett, I
9 have no more questions for you on
10 behalf of Johnson & Johnson, subject
11 to your counsel doing a direct of any
12 kind.

13 THE WITNESS: Sure. Thank you.

14 EXAMINATION

15 QUESTIONS BY MS. BOCKUS:

16 Q. Good afternoon, Dr. Plunkett.
17 You and I have met before. My name is Jane
18 Bockus, and as you know, I represent Imerys
19 in this case.

20 A. Yes.

21 Q. Correct?

22 I want to go back to just touch
23 briefly on a couple of issues that have
24 already been addressed.

25 Would you agree that IARC has

1 not classified any of the heavy metals that
2 you've identified in your MDL report as
3 carcinogenic to the ovary?

4 A. So the answer is I'd have to
5 look. I don't recall that, but I'd have to
6 look to confirm.

7 Q. Okay.

8 A. That's the answer I believe I
9 gave a few minutes ago, yes.

10 Q. So if I look at the IARC
11 website, then I can confirm whether or not
12 they have identified any of those as
13 carcinogenic to the ovary?

14 A. Not so much the web -- well,
15 the website or the actual documents. I think
16 I would actually point you to the actual
17 monograph --

18 Q. To the monograph.

19 A. -- because there may be
20 evidence in there of ovarian cancer as being
21 seen in studies. And I'd have to go look.

22 Q. Okay. That was not part of
23 your consideration here, correct?

24 A. So ovarian cancer is part of my
25 consideration, but I didn't -- in this part

1 of my evaluation I'm trying to -- trying to
2 describe these metals. And this is really
3 about mechanism of biologic plausibility and
4 the fact that these two things can go
5 together, and then the concept of additivity
6 is they're on hazard. The idea if you have a
7 cancer hazard generally and you have similar
8 mode of action, regardless of the tissue, you
9 would be expected to have a potential
10 additive effect when you do a risk
11 assessment.

12 So that's my use of that data,
13 which is why I didn't do a separate ovarian
14 cancer assessment for each of the each
15 constituents but just on powder.

16 Q. And you discuss that topic on
17 page 47, paragraph 68, of your report,
18 correct, the -- whether there's an additive
19 effect?

20 And you cite to Casarett and
21 Doull. I don't know if I'm pronouncing those
22 names correctly.

23 A. I'm sorry, on what page?

24 Q. I'm on page 47, paragraph 68.

25 A. Okay. Sorry. I should know

1 where it is, but...

2 Okay. I'm there, yes. Okay.

3 Yes, I do cite to a chapter in
4 Casarett and Doull, yes.

5 Q. Okay. And Casarett and Doull
6 is a resource that you cite to for a couple
7 of different toxicological principles that
8 you discuss in your -- in your report,
9 correct?

10 A. Yes, because it's one of the
11 most well-recognized textbooks that is used
12 across different either universities or
13 schools or even in regulatory agencies.

14 I would also say I cite EPA
15 2000 there. I'm not citing just Casarett,
16 but I am citing Casarett as well as an EPA
17 guidance document.

18 Q. In Casarett and Doull, do they
19 actually discuss talcum powder in Chapter 2,
20 or is it more just the concept of the
21 potential of the effects when you have two
22 different chemicals that you're exposed to at
23 once or three or four?

24 A. It's the latter. It's the --
25 because you'll notice the title is

1 "Principles of Toxicology," so it's the
2 general chapter teaching principles for risk
3 assessment and toxicology as used in risk
4 assessment.

5 Q. And whether there is an
6 additive effect of, say, talc and nickel,
7 that's something that an experiment could be
8 designed to study, correct?

9 MS. PARFITT: Objection.

10 THE WITNESS: If you're talking
11 generally for cancer and not worried
12 about the issue of ovarian cancer, if
13 you're talking about cancer, like
14 doing an inhalation experiment to look
15 what happens to the lung, that you
16 could do.

17 The problem with the animal
18 studies and ovarian cancer due to
19 perineal exposure is it's very
20 difficult to understand how you design
21 a study to expose the animals that way
22 reliably in the way that humans are
23 exposed.

24 But generally you could
25 study -- you might even be able to do

1 a genetically susceptible mouse study
2 to hurry the process along to look at,
3 but you might not be able to do it
4 through perineal exposure. You might
5 have to do it through another route
6 such as either inhalation or maybe
7 even you could -- you could look at it
8 through intraperitoneal injections,
9 for example.

10 QUESTIONS BY MS. BOCKUS:

11 Q. Well, and what the textbook
12 talks about is the fact that you need to
13 study it to find out whether the effects are
14 additive, whether the effects are something
15 that multiply the risk, you know, so that the
16 two together are greater than either one
17 alone, or do the effects offset each other
18 and reduce the risk, correct?

19 A. That is discussed there --

20 MS. PARFITT: Objection.

21 THE WITNESS: -- which is why
22 I've cited the EPA document. Because
23 the EPA document addresses the issue
24 of mixtures, and this is the issue of
25 mode of action. If you have chemicals

1 that you're looking at on the issue of
2 additivity or no effect, you will --
3 you look at that issue of how they're
4 affecting the tissue and underlying
5 mechanism.

6 But the only way to look at the
7 magnitude absolutely of how the risk
8 would change is by doing an
9 experiment. That is true.

10 QUESTIONS BY MS. BOCKUS:

11 Q. And to your knowledge, that
12 experiment has never been done; is that
13 correct?

14 A. I can't guarantee that it's
15 only been done for nickel and talc alone, but
16 I would -- I would state that based on --
17 there are studies out there that have been
18 done where they've used the body powder that
19 we know have metals -- a variety of things
20 within it that are not just platy talc, but
21 those experiments are that kind of data.

22 But as far as gathering
23 dose-response information or teasing out
24 individual components, that is not available.

25 Q. Do you agree that dose response

1 is the fundamental principle of toxicology
2 that underpins the effects that chemicals can
3 have on living organisms?

4 A. When you're talking general
5 toxicology, yes, I think it's talked about in
6 the textbook.

7 Q. And you agree that it is the
8 dose of the chemical and the pattern of
9 exposure that determines whether a chemical
10 produces an adverse effect on an organism,
11 not simply the presence of the chemical?

12 A. For a typical dose-response
13 relationship for non -- for nongenotoxic
14 events, absolutely, I would agree that is
15 probably true. And I don't mean nongeno --
16 noncancer events.

17 In the issue of cancer biology,
18 some of those issues don't hold all the time.
19 In other words, there are certain chemicals
20 and certain ways of looking at cancer risk
21 assessment where you can't assume where the
22 threshold is or identify what a safe dose
23 would be. But certainly I agree on the issue
24 of noncancer risk assessment generally, or
25 general end points of toxicity, that is true.

1 Q. And again, do you agree that in
2 general toxicology the effects that might be
3 reported at high doses will not occur at
4 lower doses if the concentration at the site
5 of action falls below the threshold for
6 toxicity?

7 A. Yes, that could -- that could
8 be possible, yes.

9 Q. And do you agree that
10 evidence-based toxicology and epidemiology
11 dictates that the dose of the chemical is the
12 critical factor when examining the risk posed
13 by a chemical, not just its presence even in
14 the human body?

15 A. I would say that's generally
16 true, yes, which is why I have attempted to
17 look at the dose-response relationship as
18 well as the prevalence of the contact.

19 Q. And with regard to the human
20 studies that you cite, would you agree that
21 none of the studies that you cite in your
22 report that have to do with migration of
23 particles within the genital tract of the
24 female involve applications to the perineum
25 or outside of the genital tract?

1 A. That is true with the exception
2 of Parmley and Woodruff, which addresses this
3 issue of --

4 MS. PARFITT: Objection.

5 THE WITNESS: Talks about the
6 issue of exposure from the outside to
7 the inside.

8 But the data that is collected
9 with the different studies they have
10 deposited at some point -- at some
11 position within the vagina, that is
12 true.

13 QUESTIONS BY MS. BOCKUS:

14 Q. And that is not how talc is
15 deposited in women who use it regularly in
16 their daily routine, correct?

17 MS. PARFITT: Objection.

18 Misstates the evidence.

19 THE WITNESS: So I would say
20 that depends on what women are doing.
21 Perineal application, for example,
22 application on the underwear, can lead
23 to contact of the vaginal opening
24 depending on the woman.

25 For example, a woman who has

1 a -- had many children has a tract
2 that is stretched. There, indeed, you
3 can have more direct contact than you
4 can with a very tight -- so I would
5 say it depends on the woman and it
6 depends on the situation.

7 But I do think it's generally
8 accepted, based on my review of the
9 literature, that there is the
10 opportunity for exposure internally
11 from perineal application.

12 QUESTIONS BY MS. BOCKUS:

13 Q. And if I understand what you
14 testified to earlier today and yesterday, you
15 don't have any data that would advise on --
16 out of the talc that is deposited in the
17 underwear, what percentage of it makes it
18 into the reproductive tract?

19 A. That's the data that's missing,
20 that is true. And unfortunately, no one has
21 done a study. It would be -- if there was a
22 way to do that, it would be interesting to do
23 that. I just don't see how you design that
24 study, especially knowing the hazard of talc
25 at this point. I think that would be a

1 difficult study to get approval for.

2 Q. And do you have an opinion as
3 to whether it is even correct that each day
4 that a woman uses talc in her underwear, that
5 some of the talc makes its way to the ovary?

6 MS. PARFITT: Objection. Form.

7 THE WITNESS: Have I -- can I
8 quantify that?

9 No, I haven't quantified it. I
10 think I got asked that earlier. I
11 can't quantify the amount that gets
12 there. Or, I'm sorry, I may have
13 misheard the start of your question.
14 I apologize.

15 QUESTIONS BY MS. BOCKUS:

16 Q. Yeah, I'm really asking: Do
17 you have an opinion as to whether it happens
18 every single time a woman applies talc to her
19 perineal area? Does some of that talc make
20 it to her ovary?

21 MR. MEADOWS: Objection.

22 MS. PARFITT: Objection.

23 THE WITNESS: I don't think I
24 stated it quite that way, but
25 certainly I think the opportunity is

1 there with every application. And of
2 course it would depend upon the amount
3 of time that the contact may be in
4 place. But the opportunity is there.

5 So, for example, if you applied
6 it to your underwear and 30 minutes
7 later you go to the bathroom, it's
8 very possible that you will have wiped
9 away, and so that that application may
10 have taken an opportunity away. But I
11 do believe that the opportunity is
12 there based on the literature I have
13 seen.

14 And so I haven't formed the
15 opinion, though, that it's absolutely
16 every time. My opinion, I think, is
17 based on the fact that I believe that
18 there is data to indicate that
19 exposure occurs, and that with
20 routine, continual habit, sort of a
21 habit exposure, that indeed that there
22 was some migration that occurs.

23 QUESTIONS BY MS. BOCKUS:

24 Q. And is it fair to say that you
25 don't have an opinion as to whether that

1 migration occurs every day, once a week, once
2 a month?

3 MS. PARFITT: Objection. Form.

4 THE WITNESS: I haven't
5 formulated my point -- my opinion
6 quite that way; however, I do believe
7 that it is something that is going to
8 happen routinely with exposure. I do
9 believe that migration is something
10 that is going on routinely with
11 application.

12 So with applications, I do
13 believe that that is, but I can't tell
14 you that this amount has migrated on
15 this particular day with this
16 particular application, no. That --
17 the data that we have collected is not
18 there to allow us to do that.

19 QUESTIONS BY MS. BOCKUS:

20 Q. How do you define the word
21 "routinely" as you're using it in that
22 answer?

23 A. So that would be the idea of
24 repeated exposures, you know, within a week,
25 within a month, within a year. So not --

1 routine to me would not be -- would not be
2 applying it once a month one month, waiting
3 six months, doing it again, and then not
4 doing it until the next year.

5 Again, it's the idea -- some
6 people may -- routine may be during the hot
7 season of the year, they're routinely getting
8 daily exposures when it's warm, and during
9 the cold weather not applying. But then the
10 next year doing -- that's a routine for them
11 and their habits based on their pattern of
12 exposure.

13 Again, we know that talc, when
14 it -- when it migrates and gets into the
15 body, we have data to show that it is -- it
16 is able to persist in the body. The fact
17 that you may have not been exposed for three
18 months because it was cold doesn't mean that
19 you -- that that changes the fact that you're
20 still at risk with additional exposures the
21 next -- the next time that that habit
22 becomes -- comes into place.

23 So I think there's multiple
24 exposure patterns that are possible, but when
25 I use routine, it's something that people are

1 doing throughout their -- a period of their
2 life. And so it would be something that
3 happens either on a weekly basis for a good
4 part of the year. I haven't defined it with
5 a particular number, though, no.

6 Q. And my question had to do with
7 out of the number of times a given woman --
8 or an average woman uses talc, what
9 percentage of the time does talc make its way
10 into her reproductive tract?

11 A. So I don't think that
12 anybody -- anybody can point to a piece of
13 data that tells you that, but, again, it's
14 based upon the anatomy, I would expect there
15 to be the potential each time it's applied.

16 And on your question on
17 routine, when I'm talking routine, I'm
18 looking at not just frequency but also
19 duration. So when I'm talking about dose,
20 it's the fact that they do it on a repeated
21 basis for a number of -- a period of years as
22 well.

23 That's what the data shows in
24 the human studies. It's not something,
25 again, that may have been done routinely for

1 one year, but it does appear to be something
2 that's done more -- longer term than that.

3 But we can't give a number. We
4 have no threshold. We don't know exactly
5 what that minimum number is.

6 Q. Do you think that the minimum
7 number is greater than a year?

8 MS. PARFITT: Objection. Form.

9 THE WITNESS: I haven't formed
10 that opinion, no.

11 QUESTIONS BY MS. BOCKUS:

12 Q. Do you think it's greater than
13 a month?

14 MR. MEADOWS: Objection.

15 THE WITNESS: Greater than a
16 month?

17 QUESTIONS BY MS. BOCKUS:

18 Q. Yes.

19 A. One month in their life?

20 Q. One month in their life, where
21 they're using it every day for a month.

22 A. So I haven't formed that
23 opinion at this point in time, but I'd say
24 it's more likely to occur when you do it more
25 than a month. But I haven't formed an

1 opinion on a set number, no. I can't --

2 can't point you a specific number.

3 I'm not doing case-specific, so

4 I've not looked at any of those pieces of

5 information for any given plaintiff.

6 Q. And I'm just trying to get the
7 threshold.

8 A. Uh-huh.

9 Q. As I understand it, that is
10 part of a toxicological evaluation, is the
11 threshold below which there's not an issue.

12 So I think you've said you
13 don't know if it's less than a year, but you
14 think it's more likely than not that it's
15 greater than one month.

16 MR. MEADOWS: Objection.

17 QUESTIONS BY MS. BOCKUS:

18 Q. Is that fair?

19 A. No, that's not exactly what I'm
20 saying. I'm saying we don't know the
21 threshold. So as a result, I'm not of the
22 opinion that it absolutely can't -- it only
23 has to be this long.

24 What I'm saying to you is per
25 general principles of toxicology and based on

1 the human data that we have, it indicates
2 that it's more frequent than just one month,
3 but I can't tell you that it's absolutely not
4 possible.

5 That's where -- I do think when
6 you're talking about those kinds of patterns,
7 that's a case-specific issue for individuals,
8 because I think that would have to be
9 considered for each individual. But
10 certainly as a toxicologist, I'm using the
11 words "routine," "repeated," "longer
12 duration," "chronic exposure." And when I
13 defined "chronic" earlier, I talked about
14 years of exposure versus just one month.

15 That would be consistent with
16 what I have said, yes, but I'm not -- I -- I
17 certainly don't want to rule out that there
18 couldn't be somebody out there that could
19 show something different, because it may very
20 well be that there are people that you can
21 identify with the presence of talc in their
22 ovaries and all of their other case-specific
23 things that could -- could make that pattern
24 a -- make someone be able to draw a
25 case-specific, reliable conclusion.

1 But that's not my role. I
2 don't do case-specific.

3 Q. And I am simply trying to get
4 the parameters of your opinions with regard
5 to the amount of talc use one would need to
6 have before you would feel comfortable --
7 well, that in your opinion would be
8 sufficient to create a toxic environment.

9 MR. MEADOWS: Objection.

10 THE WITNESS: Well, that's a
11 different question. So toxic
12 environment could be with a much
13 shorter time exposure, okay?

14 QUESTIONS BY MS. BOCKUS:

15 Q. Right.

16 A. So but if you're talking
17 about -- the opinion that I have formed has
18 to do with an increased risk of ovarian
19 cancer. So with that opinion, that's the
20 description, I believe, I was giving this
21 morning. It's the idea that the data that
22 I've seen indicates that my opinion that
23 perineal use of talc body powder products
24 increases your risk for ovarian cancer above
25 that background level that you know exists.

1 That opinion is based on data
2 that is -- is -- the supporting data would
3 indicate that it has to be a habit, routine,
4 a chronic exposure. And so as a
5 toxicologist, I've tried to put that in
6 context.

7 I don't know what else to tell
8 you. That's the opinions I have formed to
9 date.

10 Q. A chronic -- a habit, routine,
11 a chronic exposure for years?

12 A. Well, chronic --

13 MR. MEADOWS: Objection.

14 THE WITNESS: -- is defined as
15 years, typically, by a toxicologist,
16 and so that's what I -- that's what I
17 told you.

18 QUESTIONS BY MS. BOCKUS:

19 Q. Shifting to your regulatory
20 opinions, you would agree that Imerys is a
21 raw material supplier to J&J; is that
22 correct?

23 MR. MEADOWS: Objection.

24 THE WITNESS: I would call them
25 an ingredient supplier, yes.

1 QUESTIONS BY MS. BOCKUS:

2 Q. Okay. An ingredient supplier.
3 And you agree that Imerys does
4 not sell any products to the general public,
5 correct?

6 MR. MEADOWS: Objection.

7 THE WITNESS: I don't know
8 that's definitely true, but I'm not
9 aware that they do.

10 QUESTIONS BY MS. BOCKUS:

11 Q. And what Imerys supplies to
12 Johnson & Johnson is not a finished cosmetic
13 that is ready to be sold on the market,
14 correct?

15 MR. MEADOWS: Objection.

16 MS. PARFITT: Objection.

17 THE WITNESS: I don't know that
18 I can answer that except in the
19 context of Johnson & Johnson's baby
20 powder, SHOWER TO SHOWER® and Shimmer,
21 it's my understanding that Johnson &
22 Johnson mixes -- has some fragrance
23 added to the talc.

24 I don't believe Imerys does
25 that, but I don't know for sure.

1 So based on what I know -- I'm
2 telling you what I know, and I would
3 call them, again, an ingredient
4 supplier, and I would call Johnson &
5 Johnson a cosmetic manufacturer.

6 Does that answer the question?

7 QUESTIONS BY MS. BOCKUS:

8 Q. It does.

9 Would you agree that the
10 minerals that you have identified in your
11 report, that the documents that you have
12 seen, would classify their -- to the extent
13 that they are ever in the powder, that
14 they're trace ingredients?

15 MS. PARFITT: Objection.

16 MR. MEADOWS: Objection.

17 THE WITNESS: So which
18 ingredients are you referring to?

19 So some of the metals, no, are
20 not trace ingredients.

21 Are you talking about the --
22 are you talking about the -- like the
23 presence of tremolite or the presence
24 of chrysotile --
25

1 QUESTIONS BY MS. BOCKUS:

2 Q. No. No, I'm sorry. I'm
3 talking about the three metals that you
4 identify in your report. Those are trace
5 elements that are -- that are sometimes
6 detected in the studies of the -- of the
7 talc.

8 MR. MEADOWS: Objection.

9 THE WITNESS: It's not how I
10 would say it. I would say they're
11 heavy metal components that are
12 naturally occurring within the product
13 that are sometimes -- sometimes
14 detectable at levels that are reported
15 as trace based on the detection limit
16 within the analysis, but at other
17 times they're not listed as trace.
18 They're actually listed with a
19 specific amount.

20 So that's what -- how I would
21 define what I call trace. Usually
22 that's how it will be reported in the
23 lab, trace, which means below the
24 limit of quantification, but it's
25 there. You're detecting it.

1 I would agree that -- that
2 there are other descriptions of heavy
3 metals in the heavy metal literature
4 that talk about trace amounts being
5 found in -- naturally occurring in
6 food, for example, and I agree that
7 that does occur. But in the case of
8 this product, we actually have
9 often -- we actually have a -- a limit
10 that is set for acceptability in the
11 specification.

12 And so I would think it's more
13 proper to call it a level of the heavy
14 metal that is allowable by the purity
15 specifications set by the product.
16 And sometimes those levels may be
17 above, and most of the times those
18 levels are below, which is why it's
19 cleared. Because I've seen some
20 analyses where different products may
21 have been, I guess, turned away or
22 considered not acceptable based on the
23 analysis of certain types of minerals
24 or metals.

25

1 QUESTIONS BY MS. BOCKUS:

2 Q. Have you seen any studies where
3 women's blood has reflected the presence of
4 nickel or cobalt or chromium?

5 MR. MEADOWS: Objection.

6 QUESTIONS BY MS. BOCKUS:

7 Q. Who are parts of these
8 studies -- these ovarian cancer studies?

9 MR. MEADOWS: Objection.

10 THE WITNESS: The
11 epidemiological literature you're
12 asking me?

13 QUESTIONS BY MS. BOCKUS:

14 Q. Yes, ma'am.

15 A. It's possible in the Nurses'
16 Health Study that we can go to that, because
17 I know they do collect some heavy metal
18 levels. I've done that for other clients on
19 other issues.

20 Most of the others, I doubt
21 that we have heavy metal levels in blood.
22 But certainly there are levels of heavy metal
23 in blood, especially things like lead, for
24 example, that we have very limited capacity
25 to eliminate.

1 So whether or not you carry
2 around a significant body burden of a heavy
3 metal in your blood is somewhat driven by the
4 exposure pattern you get. It's something
5 that's commonly -- or can you excrete it
6 quickly or not. So...

7 Q. And are you familiar with any
8 studies that have suggested that the use of
9 body powders leads to a heavy burden of
10 nickel, chromium or cobalt in the blood?

11 A. So I have not seen such
12 analysis done, no, I have not.

13 Q. In paragraph 67 of your report,
14 which is on page 46 -- I'm sorry, on -- oh,
15 I'm sorry. Paragraph 64, I apologize.

16 A. No. No, that's fine.

17 Q. It's on page 44.

18 You cite to two abstracts --

19 A. Yes.

20 Q. -- one by Fletcher and one by
21 Fletcher and Saed.

22 Do you consider these abstracts
23 to be reliable sources of data?

24 A. They're not as reliable at all
25 as a peer-reviewed article. So there's a

1 difference in the weight you give an
2 abstract, absolutely.

3 However, knowing the papers
4 that Dr. Saed has actually published in the
5 peer-reviewed literature, I have -- I have
6 mentioned them in here because I do believe
7 that they are -- they are pieces of
8 information that are highly relevant to some
9 of the issues raised in other cellular
10 studies, and so that's why they're here. But
11 certainly I do not give them the same weight
12 as in my assessment of overall risk.

13 And I would say that I had the
14 same opinions on risk before I had these
15 studies. Because in my original reports,
16 obviously, I have gone further than risk and
17 talked about cause, and I didn't have the
18 Fletcher studies.

19 The Fletcher studies are more
20 on the issue of biologic plausibility and
21 mechanism versus being important
22 underpinnings, for example, for a hazard
23 assessment.

24 Q. Is there any way that someone
25 reading your report could tell that you

1 attribute less weight to the abstracts by
2 Saed and Fletcher just by reading your
3 report?

4 MR. MEADOWS: Objection.

5 THE WITNESS: I don't know if
6 they could or not. Hopefully they
7 would based upon where they appear in
8 the report. They're not cited a lot
9 of other places, but they certainly
10 are cited.

11 So that's why I'm here today,
12 though. You're asking me these
13 questions; I'm telling you. That's
14 how I look at these studies. That's
15 all I can say.

16 I haven't -- I haven't,
17 certainly, as I've told you, given
18 things numerical weight throughout my
19 report.

20 QUESTIONS BY MS. BOCKUS:

21 Q. Looking at paragraph 118...

22 Well, when you were preparing
23 your report, were you careful with the
24 language that you used in it to be precise
25 and accurate?

1 A. I attempted to do that. I
2 can't tell that you there isn't something in
3 here I've missed. But, yes, I read this
4 report six or seven times before I finalized
5 it, trying to make sure that the language I
6 was using was an accurate reflection of the
7 opinion I'm expressing.

8 But it's possible, if you want
9 to point to something that you want to ask me
10 about, I can tell you whether or not that was
11 something that I would change.

12 Q. So on page 77, paragraph 118 in
13 the middle of it, you say, "Based on the
14 knowledge available by the 1950s, talc body
15 powders manufactured and sold by Imerys and
16 Johnson & Johnson."

17 And that's the question that I
18 have for you.

19 A. I see what you're saying.

20 Q. Was Imerys selling anything to
21 Johnson & Johnson in the 1950s?

22 MR. MEADOWS: Objection.

23 THE WITNESS: I'm thinking.

24 It's possible they did not. That may
25 be true.

1 QUESTIONS BY MS. BOCKUS:

2 Q. Well, and actually --

3 A. You know what? When I wrote
4 this sentence, I assumed that they did, but
5 if that is not true, then certainly this
6 sentence should be just Johnson & Johnson.

7 Q. Well, earlier in your report,
8 in a footnote you indicate that Imerys began
9 supplying talc to Johnson & Johnson in 1989
10 or the late 1980s.

11 Do you remember making that
12 notation?

13 A. So let me look. So if that's
14 an inconsistency, then that should change.
15 Let me look.

16 Q. And that's all I want to know,
17 if it's an inconsistency, should it change.

18 A. If it is an inconsistency --
19 certainly if Imerys was not selling talc to
20 Johnson & Johnson in 19 -- the 1950s, then --
21 then certainly Johnson & Johnson's products
22 would not -- would not be affected by Imerys'
23 activity.

24 However, if Imerys is selling
25 talc to anyone that makes a consumer product

1 in the 1950s, then -- or a precursor company
2 to Imerys is making talc that's selling for
3 body powder to somebody other than Johnson &
4 Johnson, then that opinion would still hold.

5 So -- but I certainly agree, I
6 think I -- you're right, I think I have a
7 statement about the link between the two in
8 '89. So in that case, then certainly the --
9 the link here would be related to Johnson &
10 Johnson's products.

11 Q. Okay. Yeah.

12 A. Whether or not -- if they
13 weren't sourced from Imerys, then that's a
14 separate duty on a product, not this product.

15 Q. If you look on the bottom of
16 page 7, I think you'll see the footnote I was
17 referencing.

18 And with regard to your last
19 answer, you don't have any information as to
20 whether Imerys existed and, if it did,
21 what -- who its customers were in 1950s,
22 correct?

23 A. I don't believe I do, no.

24 MS. BOCKUS: I think that's all
25 that I have. Thank you.

1 MR. LOCKE: I've got a few
2 questions.

3 EXAMINATION

4 QUESTIONS BY MR. LOCKE:

5 Q. Doctor, my name's Tom Locke. I
6 represent the Personal Care Products Council.
7 We met a couple of times before, I think.

8 A. I apologize, I don't recall
9 your name at least. The face looked
10 familiar, though. I apologize.

11 Q. I try to maintain a low
12 profile.

13 I have relatively few
14 questions. I wanted to ask you overall about
15 your opinion.

16 Would you agree that reasonable
17 scientists can disagree with your opinion
18 that talc increases the risk of ovarian
19 cancer?

20 A. I'd say I wouldn't say it quite
21 that way. I'd say that I agree that
22 scientists can disagree on conclusions they
23 draw, depending on the -- depending on the
24 way that they have assessed.

25 So certainly based on a

1 complete assessment the way I did, then I
2 would agree that other people could come to a
3 different conclusion, absolutely.

4 So I think it depends what you
5 mean by "reasonable scientist." But I would
6 agree that individuals can look at the same
7 body of data and, based on their judgment and
8 experience, based on looking at that same
9 body of data, could come to a different
10 conclusion, yes. That's true.

11 Q. You've been involved in this
12 talc litigation for at least a couple of
13 years, right?

14 A. Yes.

15 Q. And you know that various
16 defendants have offered experts who disagree
17 with your conclusions, right?

18 A. Some of my conclusions, yes. I
19 don't know that there is somebody that's in
20 the litigation that does exactly what I do
21 across all the opinions I've expressed, but,
22 yes, certain parts of my opinions there are
23 other experts I'm aware of, yes.

24 Q. Well, they -- you're aware that
25 there are defense experts who disagree with

1 your opinion that talc increases the risk of
2 ovarian cancer; is that correct?

3 A. Yes, I -- I am aware of that
4 fact.

5 Q. And in your review of the
6 records that go back or the scientific
7 materials that go back 35 years or more,
8 you've seen that there's disagreement
9 regarding that issue; is that correct?

10 A. So what documents are you
11 referring to? Are you asking me about a
12 specific -- just the published medical
13 literature? Are you asking about documents
14 like internal company documents, reviews by
15 others? What are you asking me about?

16 Q. Well, let's focus on the
17 published medical literature.

18 There are scientists who have
19 disagreed with your opinion; is that correct?

20 MS. PARFITT: Objection.

21 THE WITNESS: I'm not aware of
22 a paper in the published medical
23 literature that has done the exact
24 assessment I have done.

25 So I am aware of the fact,

1 however, that there are individual
2 papers by scientists that, for
3 example, have concluded that there is
4 no association between exposure to
5 talc perineally and ovarian cancer,
6 yes. Individual papers, I am aware of
7 that, but that's different than what I
8 have done.

9 QUESTIONS BY MR. LOCKE:

10 Q. Let me just ask you about what
11 you were requested to do on behalf of
12 plaintiff's counsel.

13 Plaintiff's counsel asked you
14 to provide opinions related to the human
15 health hazards posed by exposure to talcum
16 powder products and how those hazards relate
17 to the regulatory requirements for marketing
18 cosmetic ingredients and cosmetic products in
19 the United States; is that correct?

20 MR. MEADOWS: Objection.

21 THE WITNESS: I didn't write
22 that, but that sounds like an accurate
23 reflection of what -- what we -- what
24 I have done at least in parts of my
25 report, yes.

1 QUESTIONS BY MR. LOCKE:

2 Q. Well, if you look at your
3 report, I think you go to part where you were
4 asked to provide -- and I just pulled it from
5 what you said.

6 A. So I did write it, I apologize.
7 It didn't sound like me.

8 Q. It started with "to provide
9 opinions related to the human health hazards"
10 and so forth, so I just wanted to make sure
11 we're clear on that.

12 A. Sure.

13 Q. So does that sound right in
14 terms of what you were asked to do?

15 A. I said I -- certainly those are
16 the kinds of things that I was definitely
17 asked to do. I was asked to do two basic --
18 two basic things, which was having to do with
19 toxicology and risk assessment, and then a
20 separate issue related to regulatory
21 concerns.

22 So, yes, those are the two
23 basic, I guess, buckets of information and
24 documents that I reviewed and opinions I've
25 expressed, and I think that's consistent with

1 what I've been doing in the litigation.

2 Q. Okay. As to that second
3 bucket, the US regulatory requirements for
4 marketing cosmetic ingredients and products,
5 that's not relevant to the scientific
6 question whether talc may cause ovarian
7 cancer; am I right?

8 A. No. I disagree with that based
9 on the fact that a company that markets a
10 cosmetic product is required to do a safety
11 assessment. And if in that safety assessment
12 issues relate to cancer or ovarian cancer and
13 the use of talc, then those two things are
14 related.

15 But I would agree that -- that
16 doing a risk assessment like I've done is a
17 separate issue from doing a safety assessment
18 for a product, because there's actually even
19 a lesser standard for an issue of looking at
20 a safety assessment for a product versus
21 actually forming the opinion that there is an
22 increased risk of cancer with exposure to
23 talc.

24 Q. Now, did IARC in 2006, did it
25 look at the US regulatory process in

1 considering whether talc may cause ovarian
2 cancer?

3 MR. MEADOWS: Objection.

4 THE WITNESS: I don't think I
5 understand what you mean. It's not a
6 US regulatory process, no, if that's
7 what you're asking me.

8 They have a -- they have a
9 discussion of what the products are,
10 which is part of the way they're sold.
11 But I don't think they're discussing
12 the duty of a company under the
13 regulatory process, no, that's a
14 separate issue.

15 QUESTIONS BY MR. LOCKE:

16 Q. So their analysis of whether
17 talc may cause ovarian cancer, that's
18 different than the analysis of whether a
19 company may have a duty, whatever that duty
20 may be?

21 MR. MEADOWS: Objection.

22 THE WITNESS: It's a different
23 process, absolutely. IARC is a
24 separate, independent body that does
25 an assessment looking at the issue of

1 cancer hazard and looking at whether
2 or not there is sufficient evidence to
3 categorize that hazard, whereas a duty
4 of a company under the regulatory
5 situation is broader than just cancer
6 hazard; it's a whole different thing.
7 It's what you do internally before you
8 market a product. Totally different.

9 And so certainly when I --
10 that's why I have separate sections in
11 my report, and that's why I even
12 have -- I've had discussions about the
13 difference between the regulatory
14 standard for warning versus the
15 assessment of risk that may be
16 required in order to start to produce
17 a -- identify a association or an
18 increased risk or even if you did a
19 causation analysis. Totally different
20 type of exercise.

21 QUESTIONS BY MR. LOCKE:

22 Q. Do you first, in that exercise,
23 look at the scientific issue of whether talc
24 may cause ovarian cancer?

25 A. Are you asking me in either of

1 these exercises?

2 Q. Well, let's say when you're
3 getting to -- you mentioned the duty to warn.
4 So if you're looking at the duty to warn, do
5 you first have to look at does talc cause
6 ovarian cancer?

7 MR. MEADOWS: Objection.

8 THE WITNESS: That's not the
9 question you asked. No. I would
10 argue, based on the regulations, if
11 you look at the standard, the question
12 is, is there evidence to indicate that
13 there is a chance, there is a
14 potential -- not that it does, but is
15 there a potential for that type of
16 hazard to be posed to consumers who
17 use the product.

18 It's a possibility versus being
19 a -- I'm taking it beyond possibility
20 when I'm doing my assessment for
21 increased risk. And I talked about
22 that this morning, and I can't
23 remember her last name. The
24 Johnson -- I apologize. But I -- with
25 Johnson & Johnson. I talked about

1 this is a different assessment and
2 different standard. It's a much lower
3 standard on cosmetics for what needs
4 to be done as far as warning.

5 Now, when a company comes and
6 initiates a safety assessment on their
7 product, before they even think about
8 what am I going to warn, they should
9 be doing a comprehensive assessment of
10 safety based on what's available
11 publicly, knowing what others have
12 reported and then what data they've
13 collected.

14 If they don't have data at all
15 on the safety of the product, then the
16 product has to say that. We don't
17 know. We do not know if this product
18 is safe. And that's one of the things
19 that is allowed under FDA -- under FDA
20 regulations as well.

21 But essentially some -- some
22 assessment must be done to understand
23 from the perspective of the company
24 that this product is safe for
25 consumers to use as -- under the

1 directions of use.

2 So in the case of this, it
3 would be a body powder being used on
4 the body surface but also perineally
5 because -- because that was an
6 exposure pattern that was understood.

7 QUESTIONS BY MR. LOCKE:

8 Q. Okay. You described two
9 different buckets. They're independent
10 assessments; is that correct?

11 MR. MEADOWS: Objection.

12 THE WITNESS: Initially that's
13 where I started, and now I'm talking
14 two different duties. There's a duty
15 to warn, but there's first a duty to
16 collect information before you market
17 it. It's your premarket safety
18 assessment.

19 QUESTIONS BY MR. LOCKE:

20 Q. Okay. I'm not actually talking
21 about the manufacturer's duty. I wanted to
22 just first address your scientific analysis.

23 That's a separate question that
24 led you to your opinion on the -- your
25 opinion that talc increases the risk of

1 ovarian cancer, correct?

2 MR. MEADOWS: Objection.

3 THE WITNESS: Yes, that's what
4 I described. And I thought you were
5 talking about duty of the company, and
6 so I apologize. I didn't mean to go
7 off on a tangent.

8 If you want to focus just on
9 the risk assessment -- is that what
10 you want to do? -- that's what I'm
11 doing.

12 QUESTIONS BY MR. LOCKE:

13 Q. No, I just want to understand,
14 those are two different things, though,
15 right?

16 A. Those are two different --
17 those are two different tasks that I
18 undertook, yes. I undertook a risk
19 assessment task to form opinions based on
20 what I can say about risk, and then I
21 separately -- and I had done this earlier on
22 the issue of warnings, looking at what do we
23 know about the product and whether or not --
24 and when did we know it, and what should
25 consumers have been warned about based on the

1 safety information that was available over
2 time.

3 Q. The risk assessment task,
4 that's what you mean by your analysis that
5 talc increases the risk of ovarian cancer?

6 A. That's correct.

7 Q. You could have stopped at that,
8 but then you performed an additional task; is
9 that right?

10 A. Well, actually, no, because the
11 first task I actually started with was the
12 regulatory task. When I first started
13 getting involved in the litigation very --
14 before I wrote my first report, one of the
15 first things I was looking at was the issue
16 of the duty of the manufacturer to provide
17 warnings.

18 And then after that, I expanded
19 that role to be an inclusion as well of a
20 causation analysis.

21 And then now I'm not doing a
22 full causation analysis in this litigation,
23 but I'm using essentially some of the same
24 information to provide you with a description
25 of a -- a health risk assessment, which was

1 also sort of -- that's a piece along the way
2 to doing a causation analysis, but it's not
3 the same.

4 Q. Your opinion regarding the
5 FDA's responsibilities and functions, that's
6 not related to your opinion that talc may
7 cause an increased risk in ovarian cancer; is
8 that correct?

9 MR. MEADOWS: Objection.

10 THE WITNESS: I don't think
11 that's true the way you're asking that
12 question, because I don't know how you
13 divorce the fact that as a -- in a
14 regulatory assessment, if I identify
15 cancer hazard, I have identified a
16 duty to warn. That's certainly
17 something that should be warned about
18 when I understand that there's not
19 only the potential, but I believe
20 there's an increased risk.

21 But I would agree with you that
22 in my report, I'm laying out for you
23 even different bodies of information
24 that -- as I step through it.

25 Does that make sense to you?

1 QUESTIONS BY MR. LOCKE:

2 Q. Not really.

3 A. I'm sorry.

4 Q. I'm talking about your
5 scientific analysis here, not your regulatory
6 analysis.

7 To do your scientific analysis,
8 you looked at scientific materials, right?

9 A. Yes, but I do the same thing
10 for my regulatory analysis. That's why I'm
11 confused. I -- to me they are connected.

12 But I would agree with you, I
13 had an analysis. Let's just talk about that,
14 my analysis on risk assessment and my
15 opinions that I've expressed. Those are laid
16 out in a separate section of my report,
17 absolutely. So we could talk about that if
18 you'd like.

19 Q. Well, I just want to
20 understand, and I think I do now, that's a
21 separate issue from your regulatory opinion?

22 A. It's not a separate issue.
23 That's where I'm having trouble with your
24 language.

25 It's a separate task because,

1 for example, I may have only been asked, but
2 I wasn't, to just describe whether or not, as
3 a human risk assessor and toxicologist, there
4 is a hazard or a risk posed by the product,
5 and I could stop there.

6 But I was asked, based on --
7 based on my experience working in the area of
8 regulatory toxicology but also on regulatory
9 issues for clients where I give advice, I was
10 asked to look at how does that scientific
11 information impact what the company should be
12 doing.

13 And so that's -- that's why I'm
14 saying you can't divorce them, because the
15 warning issue I'm talking about is intimately
16 tied into the human health risk assessment
17 results.

18 Q. So do you consider yourself
19 primarily here as a warning expert?

20 MR. MEADOWS: Objection.

21 THE WITNESS: I consider that
22 one of my roles, yes, absolutely.

23 It depends upon how individual
24 cases, individual attorneys, will --
25 will ask -- decide to use me. For

1 example, I have been used in one trial
2 to only talk about the toxicology.
3 Other trials, I've talked about
4 toxicology as well as regulatory
5 issues. So I think it just depends on
6 the case.

7 In the MDL, I am prepared,
8 however, to come to talk at a trial on
9 the regulatory system that guides
10 cosmetics as well as provide opinions
11 that talk about what are the hazards
12 of talc, what is the toxicology of
13 talc, what do -- how can you be
14 exposed to talc, that migration issue,
15 and then my opinions about whether or
16 not I believe that there is an
17 increased risk of ovarian cancer.

18 So I would be -- be prepared to
19 talk about both of those things.
20 That's why I said I do think I'm a
21 little different than some of the
22 other experts that you may encounter,
23 for example, in the defense side,
24 where someone may just do regulatory
25 or somebody may just do toxicology.

1 But I practice in both those areas in
2 my consulting practice and in my
3 experience.

4 QUESTIONS BY MR. LOCKE:

5 Q. Let me ask you a few questions
6 about your cosmetic ingredient review
7 statements, CIR.

8 We can agree to call it that,
9 right?

10 A. Yes, that's fine.

11 Q. In parts of your report, you
12 cite the CIR as an authoritative source on
13 cosmetic ingredients; is that correct?

14 A. So where are you looking at,
15 the background information on the CIR?

16 Yes, they certainly are a
17 source of information that FDA relies upon as
18 far as assessments, yes, that's true.

19 Q. Well, and on page -- or
20 paragraph 35, page 23, you cite to the CIR
21 on, for example, chemicals purportedly in
22 cosmetics. You have a footnote there.

23 A. So --

24 Q. I believe it's footnote 31.

25 A. Yes, I have looked at -- looked

1 at the CIR as a source of information because
2 many of the chemicals, many of the
3 ingredients within the fragrance of Johnson &
4 Johnson, the only available information may
5 be found within the CIR that's publicly
6 available.

7 Q. And you rely on the report of
8 Dr. Cralley; is that correct?

9 MR. MEADOWS: Objection.

10 MS. PARFITT: Objection.

11 QUESTIONS BY MR. LOCKE:

12 Q. You reference Appendix D to
13 your report. I believe if you stay on the
14 same page you'll see that, the same
15 paragraph.

16 A. I wouldn't say I rely on the
17 report of Dr. Cralley because I form my
18 opinions independent of Dr. Cralley, but
19 certainly his -- I believe if you go to his
20 reports, his report is supportive of my
21 opinions in this area.

22 Q. Did you read his report?

23 A. I have read it now, but I did
24 not read it before I -- before I formed my
25 opinions in this particular paragraph, yes.

1 Q. I'm a little confused because
2 you're citing to his report.

3 You read it or you didn't read
4 it before you wrote this paragraph?

5 A. I read it before I wrote the
6 paragraph. I didn't read it before I had
7 formed the opinion. Do you understand what
8 I'm saying?

9 I did my review of the irritant
10 chemicals independently before I looked at
11 Dr. Cralley's report. So I had formed the
12 opinion that -- of the chemicals I had
13 searched for that this is what I identified.
14 And that's what this is talking about, right?

15 I'm saying here that of the
16 more than 100 chemicals included, over
17 70 percent are compounds linked with some
18 level of irritant hazard. That was done on
19 my own.

20 Then, if you go to look at
21 Dr. Cralley's report, I cite it here because
22 it's consistent. That is, his report
23 provides support additionally for the
24 statement I'm making.

25 So I'm not relying on his

1 conclusions to make my opinion, but it's
2 certainly -- I am citing it here as it being
3 a piece of evidence that is consistent with
4 my opinions.

5 Q. Sorry, I seem to have messed up
6 my microphone. I'll try to hold it for a
7 little bit then.

8 Do you disagree with
9 Dr. Cralley's report?

10 A. I have not formed an opinion
11 that I agree or disagree. He -- with his --
12 I believe he has information that is
13 consistent with the opinion I'm expressing in
14 the sentence, however.

15 Q. And do you know that
16 Dr. Cralley repeatedly cites to the CIR as an
17 authoritative source regarding cosmetic
18 ingredients?

19 A. I don't know that he uses that
20 exact language, but he does cite to it, yes,
21 in his report. Certainly he does.

22 Q. More than 20 times, right?

23 A. That, I have not counted. I
24 can't tell you that. But he does, just like
25 I do, as a source of information when there

1 is no other source available.

2 Q. Okay. In your report you state
3 that the CIR process is administered
4 independent of the FDA.

5 But the FDA is on the CIR
6 steering committee; is that correct?

7 A. That is correct.

8 Q. You don't mention that in your
9 report, although you mention others who were
10 on the CIR steering committee, correct?

11 A. Yes, there's a paragraph where
12 I talk about others, yes.

13 Q. But you don't mention that the
14 FDA is on the steering committee?

15 A. I believe I -- I believe I've
16 been asked that question before, and I said
17 yes, but certainly in this report I don't
18 believe I state that, that is true.

19 Q. CIR solicits input from the
20 public; is that correct?

21 MS. PARFITT: Objection.

22 THE WITNESS: I would say they
23 solicit input from industry, yes.

24 QUESTIONS BY MR. LOCKE:

25 Q. Well --

1 A. But they -- and they do have a
2 public comment period, which is mainly input
3 from industry.

4 But I agree that they do -- and
5 if what you're referring to is a public
6 comment period, yes, there is that for the
7 documents.

8 Q. You can go on the website and
9 see what ingredients CIR is going to review,
10 right?

11 A. Yes, you can.

12 Q. Have you done that?

13 A. Yes, I've done it many times
14 before.

15 Q. Okay. And did you submit
16 comments on talc in 2012?

17 A. No, I did not.

18 Q. Okay. You could -- the public
19 can submit comments many times during the
20 process of an ingredient review; is that
21 correct?

22 A. There are different --
23 different stages of the draft document. Is
24 that what you're asking me? Yes, that can be
25 done.

1 Q. Well, even before it's a draft,
2 CIR is soliciting information about the
3 ingredient to include in the initial
4 materials provided to the expert panel; isn't
5 that correct?

6 A. Technically I believe that is
7 true, but I would disagree that that is
8 something that happens routinely. But I
9 would agree that -- I would say technically
10 you may be -- that is something that could
11 occur, yes, but that is not the situation,
12 for example, in the case of talc.

13 Q. Why not?

14 A. Based upon what I have seen
15 described as how the review was done, and
16 that has to do with the testimony of
17 different -- or different documents that I've
18 reviewed and the testimony of individuals
19 related to this document.

20 Q. Well, Dr. Cramer could have
21 submitted comments to the CIR regarding talc,
22 couldn't he?

23 MR. MEADOWS: Objection.

24 MS. PARFITT: Objection.

25 THE WITNESS: You'd have to ask

1 Dr. Cramer if he was aware that they
2 were reviewing it. I can't answer
3 that for Dr. Cramer.

4 But if he was aware of it,
5 certainly -- if you're aware of the
6 process going on and the timing of it,
7 certainly you can submit comments.
8 I'm not disagreeing with you on that.
9 That is true.

10 QUESTIONS BY MR. LOCKE:

11 Q. CIR publishes in advance what
12 it's going to review; isn't that correct?

13 A. What is coming up for review?

14 Q. Yes.

15 A. Yes, things that are proposed
16 for the next meeting, yes, that's true.

17 Q. And you could submit comments
18 to the first draft of the CIR report; isn't
19 that correct?

20 A. I would agree that that is
21 possible to happen, yes.

22 Q. And you can submit comments
23 before the final report is drafted, correct?

24 A. Yes, as long as it's still in
25 draft form, yes, those comments can be

1 submitted.

2 Q. And CIR meetings are open to
3 the public, right?

4 A. That is true, they are open to
5 the public, but in my experience it -- they
6 are not meetings that are heavily attended by
7 the public but indeed are -- tend to be
8 meetings attended by industry stakeholders
9 within the ingredients that are being
10 reviewed.

11 Q. You know Mr. Steinberg here.
12 He was a plaintiff's expert for a while?

13 A. I don't know him personally,
14 but I know his name and I know he was a
15 plaintiff's expert, yes.

16 Q. You know he attended the talc
17 meeting, right?

18 A. Yes, I believe he was working
19 with indus -- he works with industry, so I
20 believe indeed he did attend that meeting.

21 Q. You're not claiming he was
22 working with any industry member regarding
23 talc, are you?

24 A. That's not what I stated. I
25 know he's a consultant to the cosmetic

1 industry, so it doesn't surprise me. And I
2 believe he lives in the area, so it doesn't
3 surprise me that he attended.

4 I haven't spoken to him about
5 any of that, though, so I have no specific
6 details of that.

7 Q. Transcripts of the meeting are
8 available to the public, right?

9 A. You can download the
10 transcripts, yes.

11 Q. They're on the website?

12 A. That's what I said. You can
13 download. I'm sorry.

14 Q. Okay.

15 A. Yes, you can download them from
16 the website.

17 Q. Did you submit comments to the
18 CIR regarding talc?

19 A. No, I did not.

20 Q. Why not?

21 A. I wasn't aware of the process
22 that was going on in the draft form at the
23 time.

24 Q. Why is that?

25 A. I was not following the CIR for

1 talc at that particular time. I have a lot
2 of other clients and a lot of other issues
3 that go on on a routine basis, and I -- I
4 literally would not have time to follow every
5 assessment they do, considering that they do
6 thousands of chemicals.

7 Q. Did you know of the CIR prior
8 to your retention by plaintiff's counsel?

9 A. Yes. In fact, I -- one of the
10 journals that I receive, International
11 Journal of Toxicology, maybe, publishes many
12 of their safety assessments. So I certainly
13 am, yes.

14 I was aware -- when I was at
15 Eviron, I was aware of the existence of CIR.

16 Q. Have you ever provided prior to
17 this litigation -- and by "this litigation" I
18 mean any aspect of the talc litigation -- an
19 expert opinion on cosmetics' ingredients?

20 A. You're asking me in any other
21 litigation on a cosmetic ingredient?

22 I'm thinking back to the cases
23 I've worked on. Not as a -- not as a
24 testifying expert.

25 At Eviron, though, we worked on

1 litigation involving cosmetic ingredients,
2 thought I was not the testifying expert.

3 Q. In your report you talk about
4 the percentage of -- or the number of
5 ingredients that the CIR listed as unsafe.

6 Do you recall that?

7 A. Yes. I mean, if you want me to
8 verify the number, I need to go there. But,
9 yes.

10 Q. You don't mention that CIR has
11 put limitations on approximately 50 percent
12 of the ingredients that it has reviewed, do
13 you?

14 A. I don't mention that, but they
15 do. They have -- they have -- when they have
16 a statement about safety, they will -- they
17 will often talk about the limitations from
18 the safe use based on either concentration or
19 even maybe route of exposure, that is true.

20 Q. Why don't you do that? Why
21 didn't you include that in your report?

22 A. No particular reason. I mean,
23 the point I'm trying to make is really the
24 workload that's going on here and the
25 impossibility of the task of providing the

1 same level of review of any of these
2 ingredients as can be provided -- as was
3 provided by the IARC.

4 And so, again, that's one of
5 the comparisons I'm doing. I'm talking about
6 the difference in the time, the effort, the
7 difference in the independence of the
8 reviews. And so that -- when I'm talking
9 about, those numbers, that's what I'm
10 focusing on. I'm focusing on the fact that
11 you have so many reviews in a very short
12 period of time, with a one-expert panel, it's
13 impossible for that level of analysis and
14 review to be anywhere near what IARC panels
15 do, and also nowhere near the level of review
16 that I have done based on the number of
17 documents that I have analyzed and looked at.
18 So it's a different type of review.

19 Q. Let me ask you a few questions
20 because you have criticized the panel.

21 You would agree with that,
22 correct?

23 A. Yes. Oh, absolutely. This
24 particular analysis I have. I have made some
25 general criticisms of the overall process,

1 and then I made some specific criticisms of
2 this particular review.

3 Q. And one of your criticisms is
4 that the CIR -- I think you said two CIR
5 expert panelists had conflicts of interest;
6 is that correct?

7 A. Yes, that -- they did, that
8 were not -- that were not -- I believe not
9 understood even by Dr. Andersen at that time.
10 I think these are things brought up to him
11 that he was not aware of.

12 Q. All right. Now, you read his
13 testimony in one of the trials in California,
14 right?

15 A. Yes, that's the -- in fact,
16 that's the source of the information where
17 I'm citing to those names of those
18 individuals. I think I refer to that, his
19 trial testimony.

20 Q. And didn't he, though, say,
21 well, he didn't view it as a conflict of
22 interest because the money wasn't going to
23 them personally, it was going to their
24 organizations?

25 A. He did make that statement,

1 yes.

2 Q. And you disagree with that
3 statement?

4 A. I don't -- I mean, his
5 testimony is what it is.

6 Are you asking me do I disagree
7 that that's a conflict of interest?

8 I disagree that you shouldn't
9 disclose that as a potential conflict in the
10 documents that are produced, just like I do
11 when I write an article and I disclose that
12 I've had funding. I don't say what the
13 funding specifically paid for, but I've had
14 funding or support from this industry
15 individual or that industry individual.
16 It's -- it's something that just is about
17 transparency.

18 Q. So when you write articles, you
19 say that you've been paid a lot of money by
20 plaintiffs' lawyers?

21 MR. MEADOWS: Objection.

22 MS. PARFITT: Objection.

23 THE WITNESS: Well, I haven't
24 written an article that overlaps with
25 an issue that I've addressed in

1 plaintiffs' litigation, but I
2 certainly have given my conflict of
3 interest statements that relate to the
4 issue in the article.

5 I do that -- I've done that
6 with -- on my work -- several of my --
7 several of my assessments talking
8 about risks of pesticides. I've done
9 it with the work that I've done that
10 that's been sort of, I guess,
11 policy-type work on behalf of the
12 American Chemistry Council.

13 So absolutely I do.

14 QUESTIONS BY MR. LOCKE:

15 Q. Okay. You don't think it's
16 relevant that you receive 50 percent of your
17 money solely from plaintiffs' products
18 liability lawyers?

19 MR. MEADOWS: Objection.

20 MS. PARFITT: Objection. Form.

21 THE WITNESS: If it has nothing
22 to do with the issue that I'm
23 addressing in the paper, no, I do not
24 think that.

25 But when you're accepting money

1 from an industry or a company that has
2 to do with the issue you're looking
3 at, yes, a conflict -- a conflict of
4 interest absolutely needs to be
5 described.

6 QUESTIONS BY MR. LOCKE:

7 Q. And that would -- well, let me
8 just ask you: You're not an ethicist, are
9 you?

10 A. No, I'm not trained as an
11 ethicist.

12 Q. And you're not a lawyer, are
13 you?

14 A. Well, no, but I have passed the
15 patent bar, but I'm not trained as a lawyer.

16 Q. That doesn't make you an
17 ethicist, right?

18 A. No, it does not.

19 Q. Okay. Let's talk about one of
20 the people you criticized, Dr. Wilma
21 Bergfeld.

22 Did you know she was the first
23 woman who was the president -- to be the
24 president of the American Academy of
25 Dermatology?

1 A. No, I don't know her
2 personally, so, no, I did not know that.

3 Q. Did you investigate her at all
4 when you criticized her?

5 A. I wasn't criticizing her, I was
6 criticizing the CIR process for failing to
7 disclose the conflicts of interest of
8 individuals that were involved in their
9 assessment.

10 I certainly am not giving
11 personal criticism to either of those
12 individuals.

13 Q. You would agree that the
14 American Academy of Dermatology is a
15 reputable organization?

16 A. I haven't formed an opinion one
17 way or the other; however, I'm aware of them,
18 and certainly I know individuals that are
19 members of it, yes.

20 Q. Are those individuals reputable
21 people?

22 MS. PARFITT: Objection.

23 THE WITNESS: They are people
24 that practice medicine that certainly
25 I would go see. I mean, you're asking

1 me if I formed a very specific opinion
2 about them as individuals, and I
3 haven't done that.

4 QUESTIONS BY MR. LOCKE:

5 Q. Do you have any reason to
6 believe that the American Academy of
7 Dermatology is disreputable?

8 A. No. Again, I haven't formed an
9 opinion one way or the other. I'm aware of
10 the organization, and it certainly is one
11 that is -- has within its members a number of
12 people that I know that practice in
13 dermatology.

14 Q. Did you know that Dr. Bergfeld
15 was the first woman to be president of the
16 Cleveland Academy of Medicine?

17 A. To the what? What was the
18 first word?

19 Q. Cleveland Academy of Medicine?

20 A. No. Again, I'm not aware of
21 her CV specifically, other than what may have
22 been discussed -- it's possible her -- I know
23 her affiliation will be listed in some of the
24 documents as to where she is today, but I do
25 not know her CV and her history.

1 Q. Are you aware that she was the
2 first president -- or she was a president of
3 the American Society of Dermatopathology?

4 A. No. Same thing. If I'm not
5 aware of her CV, I wouldn't know that.

6 Q. How about that she was the
7 former chair to the FDA's drug -- FDA's
8 Dermatology and Ophthalmology Advisory
9 Committee?

10 A. Same answer. I don't know her
11 CV, so I have no knowledge.

12 Q. Is it your opinion that
13 Dr. Bergfeld was not qualified to chair the
14 CIR panel that considered talc?

15 A. I don't think I formed that
16 specific opinion. Instead, what I have --
17 the opinions I formed relate to the overall
18 makeup of the panel that failed to include
19 individuals with expertise that were -- that
20 are really key to assessing the safety of
21 talc. And that had to do with the issues of,
22 as I discuss it, epidemiology -- oh, I'm
23 sorry, I think I need to put this back --
24 period -- sorry. In the area of epidemiology
25 is one that I talked about it specifically,

1 and also gynecological -- gynecological
2 sciences on the issue of migration.

3 Q. You're not a epidemiologist,
4 are you?

5 A. Not by training. It's a tool I
6 use all the time, but I'm not an
7 epidemiologist by training.

8 Q. And panel members on the CIR,
9 they might have used the same tool that
10 you're using to form your opinion about talc,
11 correct?

12 MR. MEADOWS: Objection.

13 THE WITNESS: Based on what
14 I've reviewed from the minutes and the
15 write-up, I would disagree that that
16 is -- they have done -- they've used
17 the tools in the same way I have. I
18 disagree with that.

19 QUESTIONS BY MR. LOCKE:

20 Q. No, but I'm saying their
21 epidemiology could be the same background
22 that you have. You haven't reviewed who they
23 are, so you really don't really know.

24 MR. MEADOWS: Objection.

25 THE WITNESS: Well, I do

1 know -- I do know Dr. Klaassen, who I
2 believe was on the panel as a
3 toxicologist. He is not somebody
4 that -- he is not somebody that I
5 understand does a significant amount
6 of evaluation in risk assessment for
7 epidemiological studies. He has done
8 some of that, yes, I agree, but it's
9 different training than mine.

10 QUESTIONS BY MR. LOCKE:

11 Q. You're better qualified than he
12 is?

13 A. No, that's not what I'm saying.
14 I'm saying it's different background.

15 The question that I heard you
16 ask me, I believe, was directed towards the
17 differences in my background versus somebody
18 else's.

19 And I'm saying that I'm not
20 aware that he has the same background I do,
21 but there is not -- there was not somebody on
22 the panel that had specific expertise and
23 analysis of epidemiological studies as an
24 epidemiologist. And I think that's important
25 in this case where you're analyzing in a

1 causation analysis a wide variety of studies.

2 So I do think it's important.

3 Q. You're not a gynecological
4 oncologist, are you?

5 A. No, I'm not. But again, that
6 would have been an important expertise to
7 have on the panel when --

8 Q. And yet you formed your opinion
9 with --

10 MR. MEADOWS: Hold on.

11 MR. LOCKE: No. No. Go ahead.

12 You can ask follow-up questions
13 if you want.

14 MR. MEADOWS: You're
15 interrupting her.

16 MR. LOCKE: Well, I've got a
17 limited amount of time, and I've got
18 to keep moving.

19 MR. MEADOWS: Well --

20 MR. LOCKE: They're very long
21 answers to questions that I'm not
22 asking. So I -- you follow up if you
23 would like with your questions, but I
24 got to keep moving.

25 MR. MEADOWS: Well, I'm sorry,

1 but you're not going to be allowed to
2 interrupt her.

3 MR. LOCKE: Okay. Then we'll
4 go longer. If she's going to answer
5 questions I'm not asking, then I need
6 to go -- I need to be able to go
7 longer.

8 MR. MEADOWS: You're not going
9 to be allowed to interrupt her.

10 That's just the bottom line.

11 QUESTIONS BY MR. LOCKE:

12 Q. You're not a gynecological
13 oncologist, right?

14 A. I'm not trained as a
15 gynecologic oncologist, that is true.

16 Q. You're not a medical doctor,
17 correct?

18 A. I am not a physician, that is
19 correct.

20 Q. Let's talk about the citizens
21 petition.

22 The FDA frequently seeks
23 scientific information from cosmetic
24 manufacturers; is that correct?

25 A. First part of the question?

1 I'm sorry.

2 Q. The FDA frequently seeks
3 information, scientific information, from
4 cosmetic manufacturers; is that correct?

5 A. I don't understand what you
6 mean by "frequently seeks." They rely on
7 cosmetic manufacturers to do their own safety
8 assessments.

9 Is that what you're referring
10 to?

11 Q. Well, they ask PCPC to comment
12 on scientific issues, correct?

13 A. Yes, I would agree that that
14 interaction has happened, but that's not
15 where the responsibility lies. But I agree,
16 they have.

17 Q. I'm not asking about
18 responsibility. I'm asking: Has the FDA
19 asked cosmetic manufacturers for scientific
20 information?

21 A. Yes, they have in this case. I
22 discuss some of that, yes.

23 Q. And they do that frequently,
24 right? Not just in this case, but generally?

25 A. I can't answer that for all

1 situations. I have seen it happen before,
2 yes.

3 Q. The FDA asked, for example, for
4 then CTFA to cosponsor the 1994 workshop on
5 talc, correct?

6 A. Yes, they did.

7 Q. The FDA knew that the report
8 prepared by Dr. Huncharek and Dr. Muscat was
9 based on PCPC's retention of those
10 consultants, correct?

11 A. So what are you -- what time
12 period are you talking about?

13 Q. Well, now, there was only one
14 time that Drs. Huncharek and Muscat submitted
15 a report to the FDA regarding talc, correct?

16 A. So I need to look to confirm
17 that. Which time period are you talking
18 about?

19 Q. 2009. Citizens petition.

20 A. Oh, that is true. In the
21 citizens petition, that is true, yes. But
22 I -- but...

23 Q. I mean, it says in the letter,
24 "We're submitting a report written by Drs.
25 Huncharek and Muscat," correct?

1 A. In the cover letter from the
2 CRE?

3 Q. From -- not CRE, from PCPC.

4 A. Okay. So let -- I need to -- I
5 need to refresh my memory on the way the
6 submissions were made. I apologize.

7 Do you remember which paragraph
8 that you're referring to?

9 Q. Well, it's throughout your
10 report you're talking about the citizens
11 petition.

12 A. So it's my recollection, based
13 upon the documents that I have seen, that it
14 was not a transparent process at all times
15 that Drs. Huncharek and Muscat were being
16 identified as independent consultants and
17 were not ones that were being actually paid
18 by the industry for some of the work that
19 they did. And I think that's discussed in my
20 report.

21 Q. Well, let's break that down.

22 A. If you want me to confirm the
23 issue of the 2009 -- if you will point me to
24 where you say I discuss this, I will confirm
25 that or not.

1 Q. Well, let me break it down.

2 Citizens petition submitted in
3 2008, right?

4 A. Well, there were two: one in
5 1994 and another -- I'm sorry, 1992, and
6 another in 2008.

7 Q. Well, there are actually
8 several more than that, but let's just focus
9 on the 2008.

10 In 2008, a citizens petition
11 was submitted?

12 A. Yes, that is true.

13 Q. And PCPC responded to that
14 citizens petition in 2009, correct?

15 A. They submitted comments. Is
16 that what you're asking me? Yes, they did.

17 Q. Yes.

18 And that was a cover letter,
19 correct?

20 A. A cover letter -- that's all it
21 was was a cover letter?

22 Q. Well, attached to the cover
23 letter was a report from Drs. Huncharek and
24 Muscat?

25 A. Yes, that is true.

1 Q. And you're not aware of any
2 other document indicating that PCPC ever
3 hired Drs. Huncharek or Muscat?

4 A. So that's where I'll need to go
5 back and look at the documents, because --
6 that I have discussed. So I need to find
7 that on my paragraph.

8 If you want to go off the
9 record for a minute so I don't waste your
10 time, I will look.

11 Q. Sure.

12 A. It's up to you. Or we can stay
13 on the record.

14 MR. LOCKE: I'm fine going off.

15 VIDEOGRAPHER: We are going off
16 the record at 4:23 p.m.

17 (Off the record at 4:23 p.m.)

18 VIDEOGRAPHER: We are back on
19 the record at 4:25 p.m.

20 QUESTIONS BY MR. LOCKE:

21 Q. The question I asked: Are you
22 aware of any other document indicating that
23 PCPC ever hired Dr. Huncharek and Muscat
24 other than for the 2009 response or
25 submission to the citizens petition?

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1 A. I would have to pull this
2 document, but in paragraph 90 I make a
3 statement: A 2005 response written by
4 Dr. Muscat says -- this is not '09, this is
5 2005, and Dr. Huncharek critiqued the work of
6 Dr. Cramer, who also failed to disclose the
7 financial relation -- I'll start over.

8 Okay. So I'm sorry to repeat
9 myself, but there was a little noise.

10 You asked 2009. So the other
11 time period I have in my report in
12 paragraph 90 talks about 2005, but I'd have
13 to pull this document.

14 But I am citing to the
15 deposition of Dr. Loretz, who was a PCPC
16 employee, so I think I would need to pull
17 this in order to confirm.

18 But I see depositions of her
19 and Dr. Nicholson as talking about them
20 failing to disclose the financial
21 relationship between their work and industry.

22 Q. So if Dr. Loretz did not
23 testify that PCPC had retained Drs. Huncharek
24 and Muscat in 2005, you'd have no other
25 evidence?

1 A. I can't answer that
2 definitively, but this is what I would point
3 you to. So I'd have to pull these documents
4 to confirm, but I have -- both paragraphs 89
5 and 90 address these general issues for you,
6 but I think that's the sentence and the
7 documents that I think would be relevant.
8 But I'd have to pull them to fully answer
9 your question.

10 Q. The reason I ask the question
11 is because you frequently say "the cosmetics
12 industry" without identifying a party or a
13 person. And -- well, I'll just leave it at
14 that.

15 A. And I guess the reason I'm
16 saying I need to -- I'm questioning that it
17 doesn't have to do with PCPC is because I am
18 citing to a deposition of their employee. So
19 I need to -- I would -- to affirm it, though,
20 I'd need to -- I don't want to say that
21 100 percent the answer to your question is
22 this is the evidence, but I believe that I
23 would need to go here to confirm one way or
24 the other. But certainly I would -- this
25 raises suspicion about that for me.

1 Q. You have no evidence that PCPC
2 ever retained the Center for Regulatory
3 Effectiveness; is that correct?

4 A. I believe my evidence is hiring
5 through Imerys, but let me look to make sure
6 that is true.

7 Q. Why don't you look at page --
8 or I'm sorry, paragraph 95, page 63.

9 A. That's where I am. That's
10 where I am, so let me read what I have here
11 because it's been a while since I've read
12 this paragraph.

13 So the question is, do I have
14 in evidence this paragraph that PCPC directly
15 hired the CRE?

16 No, that is not provided by
17 this paragraph.

18 Q. Okay.

19 A. However, in this paragraph,
20 based on these documents that I'm seeing and
21 I'm -- my memory of what is discussed,
22 certainly I believe PCPC would have been
23 aware of the interaction of CRE at these time
24 points when I'm talking about this event --
25 these events.

1 Q. What evidence do you have of
2 that?

3 A. Based upon the close
4 interaction between PCPC, Imerys and Johnson
5 & Johnson throughout these time periods when
6 different actions were being taken to comment
7 or to submit information on behalf of
8 industry.

9 Q. Do you have a single document
10 you can point to or is that an assumption?

11 A. That is something I seem to
12 remember based on my review of these
13 documents, but if you need a document, I
14 would have to -- have to go and look for it.

15 Q. Sitting here today, you can't
16 recall?

17 A. I can't give you a specific
18 document as I sit here today, no.

19 MR. LOCKE: I have no further
20 questions.

21 MR. MEADOWS: Yeah, short
22 break. Maybe we're done, maybe we're
23 not.

24 VIDEOGRAPHER: We are going off
25 the record at 4:30 p.m.

1 (Off the record at 4:30 p.m.)

2 VIDEOGRAPHER: We are back on
3 the record at 4:45 p.m.

4 CROSS-EXAMINATION

5 QUESTIONS BY MS. PARFITT:

6 Q. All right. Dr. Plunkett, good
7 afternoon. I know it's been a long day.

8 Dr. Plunkett, you were asked
9 throughout the course of the day about
10 different constituents which are part of the
11 talcum powder products.

12 Do you recall those questions?

13 A. Yes.

14 Q. All right. If -- without going
15 through each and every one of different
16 constituents that we've talked about that are
17 contained or could be contained in the talcum
18 powder products, if they are present, do
19 those various constituents present and
20 provide biologically plausible evidence that
21 talcum powder products can increase the risk
22 of ovarian cancer?

23 MS. BOCKUS: Object to the
24 form.

25 THE WITNESS: Yes, which is --

1 I think I have a couple of paragraphs
2 where I talk about that issue. It has
3 to do -- there's other information as
4 well, but that is a key piece of that
5 information. And I focused on mode of
6 action and additivity. That's on
7 mechanism, biologic plausibility.

8 So the fact that you have a
9 variety of constituents that have a
10 known cancer hazard that share a mode
11 of action, that increases your
12 confidence in the biologic
13 plausibility of that relationship
14 between ovarian cancer and exposure to
15 talc body powders, yes.

16 MS. PARFITT: Thank you. I
17 have no further questions. Thank you
18 very much, Dr. Plunkett. And a happy
19 holiday to you.

20 THE WITNESS: Thank you.

21 MS. BRANSCOME: I have no
22 questions.

23 MS. BOCKUS: No questions.

24 VIDEOGRAPHER: The time now is
25 4:47 p.m. This concludes the

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1 deposition, and we are going off the
2 record.

3 (Deposition concluded at 4:47 p.m.)

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CERTIFICATE

I, CARRIE A. CAMPBELL, Registered
Diplomate Reporter, Certified Realtime
Reporter and Certified Shorthand Reporter, do
hereby certify that prior to the commencement
of the examination, Laura Plunkett, Ph.D.,
DABT was duly sworn by me to testify to the
truth, the whole truth and nothing but the
truth.

I DO FURTHER CERTIFY that the
foregoing is a verbatim transcript of the
testimony as taken stenographically by and
before me at the time, place and on the date
hereinbefore set forth, to the best of my
ability.

I DO FURTHER CERTIFY that I am
neither a relative nor employee nor attorney
nor counsel of any of the parties to this
action, and that I am neither a relative nor
employee of such attorney or counsel, and
that I am not financially interested in the
action.

CARRIE A. CAMPBELL,
NCRA Registered Diplomate Reporter
Certified Realtime Reporter
California Certified Shorthand
Reporter #13921
Missouri Certified Court Reporter #859
Illinois Certified Shorthand Reporter
#084-004229
Texas Certified Shorthand Reporter #9328
Kansas Certified Court Reporter #1715
Notary Public

Dated: 12/20/18

1 INSTRUCTIONS TO WITNESS

2

3 Please read your deposition over
4 carefully and make any necessary corrections.
5 You should state the reason in the
6 appropriate space on the errata sheet for any
7 corrections that are made.

8 After doing so, please sign the
9 errata sheet and date it. You are signing
10 same subject to the changes you have noted on
11 the errata sheet, which will be attached to
12 your deposition.

13 It is imperative that you return
14 the original errata sheet to the deposing
15 attorney within thirty (30) days of receipt
16 of the deposition transcript by you. If you
17 fail to do so, the deposition transcript may
18 be deemed to be accurate and may be used in
19 court.

20

21

22

23

24

25

ACKNOWLEDGMENT OF DEPONENT

I, _____, do
hereby certify that I have read the foregoing
pages and that the same is a correct
transcription of the answers given by me to
the questions therein propounded, except for
the corrections or changes in form or
substance, if any, noted in the attached
Errata Sheet.

Laura Plunkett, Ph.D., DABT DATE

Subscribed and sworn to before me this
_____ day of _____, 20 ____.

My commission expires: _____

Notary Public

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Exhibit 35

**UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY**


**IN RE JOHNSON & JOHNSON
TALCUM POWDER PRODUCTS
MARKETING, SALES PRACTICES,
AND PRODUCTS LIABILITY
LITIGATION**

MDL NO. 16-2738 (FLW) (LHG)

THIS DOCUMENT RELATES TO ALL CASES

**RULE 26 EXPERT REPORT OF
ARCH CARSON, MD, PHD**

Date: November 16, 2018



Arch Carson, MD, PhD

Talcum Powder and Ovarian Cancer

1. Introduction

I was asked to explain the relationship between the regular perineal use of talc-based personal hygiene products and the subsequent development of ovarian cancer in their users. I intend this report to explain this relationship. I will describe ovarian cancer, what is known about its natural history, and will present statistics regarding its incidence, prevalence and fatality. I will then describe what talc is and why talcum powder is used in personal care products. I will then present the scientific evidence linking talc-based personal hygiene products and their components with cancer, and will show how the various components of this evidence, along with other data, lead me to conclude that regular perineal application of talcum powder products causes ovarian cancer in some users, and raises the risk of ovarian cancer in all users.

2. Qualifications

I am a physician who specializes in the practice of medical toxicology. I am currently an Associate Professor at the University of Texas School of Public Health in Houston and the Program Director of the Occupational and Environmental Medicine Residency training program at the University of Texas Health Science Center at Houston. I received my medical degree from the Ohio State University and a doctor of philosophy degree in Toxicology from the Kettering Laboratory at the University of Cincinnati. I am board certified by the American Board of Preventive Medicine in Occupational Medicine, and have been in the continuous practice of medical toxicology since 1991. My professional activities have included patient care, basic and applied research, teaching of medical students, graduate students and post-graduate medical trainees, and professional consulting. I have been a program director of the NIOSH-funded Education and Research Center at the University of Texas for 19 of the last 21 years. Other major collaborations include as Liaison for the World Health Organization Collaborating Centre in Occupational Health and as environmental exposure consultant to the MD Anderson Cancer Center in Houston. My curriculum vitae is attached to this report as Exhibit A.

3. Information reviewed and methodology employed

In the preparation of this report, I have reviewed relevant published scientific and medical literature, reports and documents produced in the process of litigation, and various other documents and websites that I believed to be pertinent to the refinement or extension of my professional opinions. I applied the same methodology and scientific rigor in this research that I use in my academic and clinical practice. Documents and other sources which I considered in reaching my opinions are listed in Exhibit B, "Materials and Data Considered."

4. What is ovarian cancer?

a. What is cancer?

All types of cancer involve the uncontrolled growth and accumulation or dissemination of cells that originated from normal cells, but have been altered so that they behave differently. The many cells of a single cancer that result from this change are typically all derived from a single progenitor cell, and represent a clone of cells. When this clone

reaches sufficient numbers, the cells themselves may develop into a recognizable “mass” that is called a tumor. Tumors may cause symptoms and other health problems simply by taking up space and putting pressure on neighboring structures or blocking important fluid channels or nerves, thus disrupting normal functions of the body. Still other cancers can proliferate into the blood stream. As the number of cancerous cells increase, the biochemically active substances that they produce can also become a problem resulting in abnormal biological responses throughout the body. Some substances that might become a problem in this way include normal or abnormal hormones, enzymes, antibodies, and proteins. Cancerous cells are considered malignant if they lose their normal tendency to stop proliferating when they have filled a space or the bounds of their particular tissue type, referred to as contact inhibition. Malignant cells ignore these boundary cues and may invade other tissue spaces and organs with devastating results. They may also migrate via the blood stream or other routes to distant sites within the body where they set up a new location of tumor growth and tissue invasion. This process is called metastasis. Typically, cancers are not diagnosed until they produce sufficient symptoms or biochemical abnormalities that lead to an exhaustive diagnostic search resulting in their discovery. Occasionally, cancers are discovered accidentally as part of another investigation, e.g. a chest x-ray may find an asymptomatic lung cancer; a blood test may disclose a telltale abnormality. Still fewer cancers are discovered before they cause health problems through screening tests that are sensitive and specific enough to detect common cancers at a preclinical and hopefully highly treatable stage, e.g. routine colonoscopies to detect colon cancer, or PSA blood tests to detect prostate cancer.

b. Carcinogenesis-a two-step process

The process of normal cells becoming cancer cells is generally recognized as resulting from a two-step process.

Initiation. During initiation, a change is produced at one or more places in the DNA of a cell’s chromosomes. Because the DNA represents the genetic code that becomes duplicated and passed along to cells that arise from it, when that cell divides to produce two cells, the change to the genetic code is also duplicated and is present in both of them.

Normally, the abnormal cell that results from a change in the genetic code cannot survive because its cellular machinery is also abnormal and poorly or non-functional. Less often, if the cell is able to survive in the body, it is still abnormal and deformed, and is recognized by the body’s immune system as alien. The immune system attacks it and destroys it, and it does not survive. In the very rare instance that an alteration to the genetic material results in a survivable hereditary change that is not fatal, and which can escape the surveillance of the body’s immune system, the resulting clone may live and persist. (Coussens LM, 2002)

Promotion - Once a cancer clone has been produced, it is at risk for being discovered and destroyed by the body’s immune system, or failing to thrive in an environment for which it is not suited. Promotion is the process by which the cancer clone is shielded

from the body's defenses and is stimulated to undergo rapid growth, transforming a microscopic cancer clone into a self-sustaining symptomatic cancer over time. (Ferrante D, 2007) (Coussens LM, 2002)

Most known carcinogenesis events occur by the two-step process and involve a long latent period between the moment of the alteration in the genetic material and the recognition that a cancer is present. In human cancers, this latent period is often several months to many years in length. The latency period for ovarian cancer, generally, and for cancers induced by environmental agents is usually quite long, often >20 years. (Nadler DL, 2014) Promotion occurs throughout the latent period and stimulates the growing cancerous cells to become a recognizable cancer. A third stage in the natural history of a cancer, referred to as Progression, involves maturation, differentiation or de-differentiation and accumulation of transcriptional changes that solidify the tumor's growth rate and invasiveness. Some carcinogenic substances are initiators and some are promoters, and still others are called complete carcinogens because they are capable of initiation and promotion.

c. Ovarian cancer

Ovarian cancer is a group of cancers that arise in the ovary or in adjacent tissues. It is estimated that about 22,240 women will receive a new diagnosis of ovarian cancer and about 14,070 women will die from ovarian cancer in the United States in 2018. (American Cancer Society, n.d.) (Torre LA, 2018) Ovarian cancer ranks fifth in cancer deaths among women, and first due to cancers of the female reproductive system. Most ovarian cancers are not discovered until they have reached an advanced stage and have spread to sites elsewhere in the body. Because advanced ovarian cancers are more difficult to treat, they have a high fatality rate. For these reasons, any effective prevention of ovarian cancer or reduction in ovarian cancer risk can have a significant impact on this disease and can save many women's lives.

There are several recognized forms of ovarian cancer that are distinguished by the specific tissues from which they arise, or the microscopic characteristics of the tumor cells themselves. About 85% to 90% of malignant ovarian cancers are epithelial ovarian carcinomas, and the majority of these are of the serous type (American Cancer Society, n.d.) (Prat, 2015). Ovarian, fallopian tube, and peritoneal cancers have a similar clinical presentation and are treated similarly, and current evidence suggests that they may have a common origin, supporting a common staging system (Soong TR, 2018).

Despite significant advances in cancer diagnosis and therapies over the past several decades, there have been few changes in the incidence or fatality rates for ovarian cancer. Consequently, it is worth considering preventable environmental causes of the ovarian cancer epidemic. (Woodruff, 1979) (LA Torre, 2018)

5. What is talc?

a. General

Talc is a hydrated magnesium silicate mineral produced through a metamorphic geological process and having the generalized chemical formula $Mg_3Si_4O_{10}(OH)_2$. Some substitution of atoms occurs in variations of talc found in nature. Small amounts of Aluminum (Al) or Titanium (Ti) can substitute for Silicon, and small amounts of Iron (Fe), Manganese (Mn), Aluminum (Al) and Calcium (Ca) can substitute for Magnesium. This produces slight variations in the color, hardness and chemical properties of the mineral. Talc is the softest mineral on the Mohs Hardness Scale. (King, n.d.) It is essentially insoluble in water, but is slightly soluble in dilute mineral acids. The process seems to involve the extraction of magnesium and other cations leaving only the silicate as silicic acid and silica.

The commercial value of talc stems from its crystalline structure. Most talc is present in natural deposits as the platy form of talc, in which the talc crystals are arranged in large flat sheets running parallel to one another. These sheets are attracted to each other by weak Van der Waals forces that can be easily overcome by mechanical forces, causing the sheets to slide on each other. On the macro scale, this property gives talc its characteristic slippery feeling on the skin. The platy structure also gives talc its ability to absorb moisture and oil. Some talc is found as a fibrous crystalline structure, similar to some asbestos, also a magnesium silicate mineral. In fact, these two minerals are closely related in terms of their formation and composition. Talc deposits are often intermingled with asbestos and vice versa. (Rohl, 1974) (Rohl AN, 1976) (National Institute for Occupational Safety and Health, 2011) (Lockey, 1981)

b. Talcum Powder and Cancer.

Numerous studies have examined the cancer causing characteristics of talc. (Wild, 2006) Talc has caused cancer when implanted in various tissues and under the skin in laboratory animals. It causes inflammation and fibrotic reaction, including the chemotaxis of inflammatory immune cells, and accelerated growth and division of cells in the involved tissues (Okada, 2007). This is a normal body process that leads to the thwarting of infection and rapid healing, but in the absence of tissue injury, accelerated growth and cell division has the effect of amplifying and propagating viable genetic mutations, leading to cancer. Talc particles have been repeatedly demonstrated in ovarian tumor tissues (Henderson WJ C. J., 1971) (Henderson WJ T. H., 1979) and in inflammatory tissue in otherwise normal ovaries (Mostafa SAM, 1985). In 2006, the International Agency for Research on Cancer (IARC) evaluated the published evidence for the carcinogenicity of talc, not containing asbestiform fibers, when inhaled into the respiratory system and when applied to the perineum in personal hygiene activities. The agency concluded that talcum powder is a “possible human carcinogen” (Group 2B) when applied to the perineum, meaning that there is insufficient evidence of carcinogenesis in humans, but strong evidence in other mammalian species. IARC also concluded that there was insufficient evidence of carcinogenicity by the inhalation route (Group 3). (International Agency for Research on Cancer, 2010) Since that time,

numerous other studies have added to the data on this issue. A recent meta-analysis showed that talc workers do have an excess of lung cancers. (Chang C-J, 2017)

When implanted under the skin or into tissues of laboratory animals, talcum powder induces an inflammatory response. This reaction involves the chemotaxis of inflammatory cells of the immune system, lymphocytes, neutrophils and macrophages, the release of cytokines that promote membrane permeability and stimulate cell division. As this reaction matures over time, granulomas may begin to develop. All of this signifies that talcum powder is an effective and potent promotor of already initiated genetic alterations. (Fletcher NM M. I., 2018) (Fletcher NM S. G., 2018) (Saed GM, 2017) (Radić I, 1988) (Okada, 2007) Other studies have demonstrated the ability of these same reactions to satisfy the carcinogenic initiation step, characterizing talcum powder as a complete carcinogen. (Shukla A, 2009) (Fletcher NM M. I., 2018)

c. What about asbestos and other components in talc and talc-based products?

Talcum powder products in the marketplace have been shown to contain asbestos. (Paoletti L, 1984) (VanOrden D, 2000) (VanGosen BS, 2004) (Longo WE, 2017) Asbestos is conclusively recognized as a cause of ovarian cancers. The IARC Working Group concluded that “a causal association between exposure to asbestos and cancer of the ovary was clearly established, based on five strongly positive cohort mortality studies of women with heavy occupational exposure to asbestos, (International Agency for Research on Cancer, 2012)” and “studies showing that women and girls with environmental, but not occupational exposure to asbestos had positive, though non-significant, increases in both ovarian cancer incidence and mortality. (Acheson ED, 1982) (Fox, 1982) (Berry G, 2000) (Newhouse ML, 1972) (Reid A H. J., 2008) (Reid A S. A., 2009) (Pira E, 2005) (Magnani C, 2008) (Bertolotti M, 2008) (Ferrante D, 2007) (Germani D, 1999) (Rösler JA, 1994) The classification determined by IARC included all forms of asbestos and talc containing asbestiform fibers (fibrous talc). I have seen evidence that Johnson & Johnson’s talcum powder products contain asbestos and fibrous talc.¹

d. Carcinogenic metals in talcum powder

In addition to other related minerals, talcum powder may contain varying amounts of chromium, cobalt and nickel, metal ions that are recognized as cancer causing. These ions leach out of the talcum powder slowly over time, resulting in continuous, low-level exposure of the surrounding tissues to carcinogenic metals. (Jurinski JB, 2001) I have seen evidence that Johnson & Johnson’s talcum powder products contain nickel (Group 1

¹ Ex. 28, Hopkins Dep. (Aug. 16 & 17, 2018; Oct. 26, 2018; and Nov. 5, 2018); Ex. 47, Pier Dep. (Sept. 12 & 13, 2018); Expert Report of William E. Longo, PhD and Mark W. Rigler, PhD (Nov. 14, 2018)

human carcinogen), chromium (Group 1 human carcinogen), and cobalt (Group 2B-possible human carcinogen).²

e. Other potentially cancer-causing constituents

Johnson & Johnson's Baby Powder and Shower to Shower contain numerous ingredients that have been added to the products, i.e. fragrance chemicals, some of which have been shown to produce cancer in laboratory animals. These substances are likely to be present in very small or trace quantities, and likely present a lower level of risk than the major components, by mass. Nonetheless, any additional risks are added as part of a total risk profile. I have reviewed the report of Dr. Michael Crowley and agree with his conclusions that these chemicals may contribute to the inflammatory properties, toxicity, and potential carcinogenicity of the products.³

6. Epidemiology linking talcum powder and ovarian cancer

Many research studies have shown a strong association between talcum powder exposure and the development of ovarian cancer. (Langseth H, 2008) (Terry KL, 2013) (Schildkraut JM, 2016) (Trabert, 2016) (Berge W, 2017) (Cramer Daniel W, 2016) (Penninkilampi R, 2018)

a. What evidence links exposure to talcum powder products with ovarian cancer?

Multiple epidemiological studies have examined the link between the personal hygiene use of talc containing products and the occurrence of ovarian cancers (Booth M, 1989) (Cook LS K. M., 1997) (Cook LS e. a., 1997) (Cramer DW, 1982) (Whittemore AS, 1988) (Harlow BL W. B., 1989) (Chen Y, 1992) (Harlow BL C. D., 1992) (Rosenblatt KA, 1992) (Hartge P, 1988) (Tzonou A, 1993) (Chang S, 1997) (Heller DS, 1996) (Penninkilampi R, 2018). Talcum powder causes proliferation of human (Prat, 2015) ovarian cells in culture (Buz'Zard AR, 2007), and causes these cells to express reactive oxygen species (ROS) (Buz'Zard AR, 2007).

The research investigating the link between talcum powder exposure and ovarian cancer has been reviewed as a scientific whole at multiple stages. (Harlow BL H. P., 1995) (Ness Roberta B, 1999) (Muscat JE, 2008) (Terry KL, 2013) (Berge W, 2017) (Penninkilampi R, 2018)

Laboratory, animal and human studies support the conclusions that talc causes ovarian cancer, and have filled in the blanks that establish biological plausibility and scientific coherence. (Jaiswal M, 2000) (Balkwill Fran, 2001) (Okada, 2007) (Saed Ghassan M, 2017) (Harper, 2019)

7. Talcum powder product use

² Ex. 47, Pier Dep. (Sept. 12 & 13, 2018)

³ Expert Report of Michael Crowley, PhD (Nov. 12, 2018).

Numerous studies have interviewed women regarding their personal practices of application of talc-based powders to the perineal area. Due to variations in these practices, it has been difficult to estimate dose in order to evaluate the dose response relationship for ovarian cancer. It is also difficult to exactly estimate the quantity of talcum powder administration during personal hygiene activities. For studies that attempted to determine amount of exposure, most relied on a method of estimating the frequency of application and/or the duration of those practices, then simply multiplying to reach a total number of applications over time. (Harlow BL H. P., 1995) (Langseth H, 2008) A review of studies of perineal talcum powder or cornstarch application suggests that the use of cornstarch instead of talcum powder reduces the risk of ovarian cancer. (Whysner J, 2000)

8. Other evidence

- a. Transport of talc-containing materials from the perineum to the upper reproductive tract and body cavities has been shown to occur with startling regularity and with respect to a wide variety of particulate materials. (Egli GE, 1961) (Venter PF, 1979) (Blumenkrantz MJ, 1981) (Halme J, 1984) (Sjösten ACE, 2004) Clearly, sufficient particulate materials applied routinely to the perineum have ready access and in sufficient quantities to produce biological responses in internal tissues, including the ovaries and surrounding structures. There are a limited number of animal studies suggesting that this transport does not occur. (National Toxicology Program, 1993) These are not as compelling as the human evidence because of anatomical and physiological differences between animals and humans in this regard, as well as the overwhelming evidence in humans.

9. Conclusions and opinions

The following conclusions and opinions are expressed with respect to reasonable medical and scientific certainty and I have applied reliable scientific principles and methods to the facts in reaching them. These opinions are based upon the documents and literature reviewed and cited herein, and also upon my own professional training and experience in practice of medicine and medical toxicology.

I. Talcum powder products sold for personal hygiene use are carcinogenic.

Talcum powder is immunogenic, producing chronic inflammation in the tissues in which it sequesters, with the attraction of lymphocytes and macrophages and the ongoing local release of pro-inflammatory cytokines and reactive oxygen species. Further, all talcum powder has some component of mineral fibers that are toxic to macrophages and intensify the inflammatory response and stimulate cell growth and proliferation. The presence of asbestos, fibrous talc, carcinogenic metals and other chemicals further intensify this effect. Cohort and case-control studies have shown statistically significant associations between talc-based powder use and ovarian cancers. The presence of carcinogenic metals such as, chromium, cobalt and nickel, and toxic fragrance components in commercial talcum powder products, adds to their carcinogenic potency. Talcum powder is a complete carcinogen and can both initiate and promote the development of cancers in the tissues in which it sequesters.

II. Perineal use of talcum powder products for feminine hygiene purposes results in direct exposure to the female reproductive tract.

A proportion of talcum powder from personal hygiene applications to the perineum is transported or migrates through the reproductive tract, through the patent fallopian tubes, onto the ovaries and into the pelvic cavity. Talc particles have been identified in reproductive system structures of women who utilize talc powders. These include the uterine cervix, the endometrium, the fallopian tubes and the ovaries. Inhalation is likely a secondary route of exposure.

III. Common carcinogenic constituents of talcum powder products participate in and add to the carcinogenic process.

Naturally occurring carcinogenic components of talcum powder, i.e. asbestos, chromium, nickel, and cobalt, are liberated in bodily fluids and tissues and are free to exert their carcinogenic effects. Added substances that are toxic or carcinogenic, i.e. fragrance chemicals, may also contribute to these effects. This process is the most intense where the duration is the longest. Because the ovaries have no intrinsic elimination system, the transport of talc particles and their constituents reaches the ovaries where it stalls and sequesters. For these reasons, ovarian tissue is most at risk for the carcinogenic effect of these substances.

IV. Regular perineal application of talcum powder products causes epithelial ovarian cancer in some users, and raises the risk of ovarian cancer in all users.

Multiple case-control and cohort epidemiological studies have looked at the relationship between the perineal use of talc-based powders and the eventual development of epithelial ovarian cancer. Most, but not all, of these studies show a consistent positive relationship. When confounding and bias are exhaustively considered, the positive association remains. I conclude that the apparent cause and effect relationship between perineal talcum powder use and ovarian cancer is real, amounting to about a 30% increased risk of ovarian cancer in talcum powder product users. At the current rate of ovarian cancer diagnosis and mortality, elimination of this source of risk could result in over 3,000 lives saved in the U.S. each year.

In 1965, Sir Austin Bradford Hill published what has come to be recognized as the best collection of factors to consider for the assessment of scientific evidence that relates the causation of disease to environmental exposures (Hill, 1965). These factors include: (1) Strength of association, (2) Consistency of the evidence, (3) Specificity, (4) Temporality, (5) Biological gradient, (6) Plausibility, (7) Coherence, (8) Experiment, and (9) Analogy. Below I provide my evaluation of the scientific evidence with respect to the Hill factors.

Strength of association –Many epidemiological studies have attempted to examine the association between perineal use of talcum powder products and ovarian cancer. Most of these have been case-control studies, where women diagnosed with ovarian cancer are paired with others of similar demographic background who do not have ovarian cancer. All of these women are interviewed about their past practices and exposures, including the use of talcum powder products. The resulting data are analyzed to compute an odds ratio (OR) that describes the

likelihood of those with cancer having had greater exposure to talcum powder than those who did not. Cohort studies selected populations of women, assessing them for many factors, including perineal talcum powder use, and followed them over time counting the occurrences of ovarian cancers. These studies were then able to compute a relative risk (RR) of exposure to talcum powder resulting in ovarian cancers. Of more than 25 case-control studies in the literature, the heavy majority showed positive and significant ORs for perineal talcum powder use and ovarian cancer. The three cohort studies did not find a significant relative risk of perineal talcum powder exposure leading to ovarian cancer, but did show positive non-significant trends. Several research groups have looked at the totality of the research evidence, evaluated the published study reports, and have reanalyzed those data on a common playing field through meta-analyses. Taken in their totality, and accounting for sources of bias and differing statistical treatments, these epidemiological studies support a strong association between the perineal use of talcum powder and ovarian cancer.

Consistency of the evidence – As stated above, the majority of epidemiological studies that have investigated the link between perineal talcum powder use and ovarian cancer have reported positive associations. These studies are consistent in their findings of a relationship between perineal use of talcum powder products and the development of ovarian cancer. Further, recent meta-analyses of previously published studies have verified the comparability of the research methods used and the consensus of conclusions.

Specificity – Specificity is the concept that a specific disease, rather than a host of diseases, is produced by a particular exposure, and that the exposure is a principal cause of the disease. Although talcum powder is known to cause non-specific inflammation in many tissues where its residues locate, the stimulation of ovarian cancer is particularly associated with the presence of talc in the ovaries and fallopian tubes. Of known factors associated with ovarian cancer, i.e. nulliparous state, early menarche, late menopause, oral contraceptive use, living in the twentieth century and beyond, perineal talcum powder exposure is proving to be prominent among them.

Temporality – If a particular exposure is the cause of a particular disease, then the onset of exposure should precede the onset of the disease. Studies investigating the link between perineal talcum powder exposure and ovarian cancer are designed to compare those with prior exposure to those who are not exposed, and so the scientific evidence supports this consideration.

Biological gradient – A basic toxicological principle is that a greater exposure intensity will result in a larger proportion of those exposed expressing the toxic effect, in this case ovarian cancer. In order to determine the intensity of a long-term environmental exposure, typically a measure of frequency or quantity of use is multiplied by the duration of such use. This allows categorization of exposure levels and comparisons. Although some studies have failed to find evidence of a dose-response relationship, several more recent reports have shown a clear dose-response when the number of subjects rose to a level producing sufficient statistical power to allow the analysis after subdivision of subjects into pertinent categorical groups, and frequency and duration were measured (Schildkraut JM, 2016) (Cramer Daniel W, 2016) (Wu, et al., 2009).

Plausibility – This factor expects the rational presentation of a mechanism whereby the exposure in question leads to the disease. Thus, if no such mechanism can be proposed, it is less likely that causation will be supported. In the case of ovarian cancer, the mechanism supported in the literature is as follows: Talcum powder products are applied to the perineal area in the course of routine personal hygiene practices. This element is supported by the existence of these products in the marketplace for many years and the statements of subjects interviewed for the purpose of conducting the scientific research discussed elsewhere in this report. Portions of the applied powders are transferred via active processes or passive mass action movements into the female reproductive tract, some making it all the way to the distal fallopian tubes, the ovary surfaces and the pelvic and peritoneal cavities. This element is supported by the observations that particulate materials of differing variety can make their ways along these pathways to the listed destinations, and the finding and confirmation of talc particles in normal ovarian tissues and ovarian tumor tissues at the time of oophorectomy or autopsy. Once reaching the target tissues, talcum powder and its constituents initiate carcinogenesis via multiple means, including, inflammation with chemotaxis of inflammatory cells, liberation of cytokines, and reactive oxygen species, inactivation of TP53 genetic modulator, inhibition of DNA repair, and long-term promotion of genetic mutations via continuous inflammation and cellular growth stimulation.

Coherence – The proposed cause and effect relationship should not “seriously conflict with the generally known facts of the natural history and biology of the disease.”(Hill, 1965) The proposal that talcum powder product use results in the occurrence of ovarian cancer is entirely consistent with what is known about other factors related to ovarian cancer, i.e. early menarche, late menopause, pregnancies, breastfeeding history, oral contraceptive use, etc. All are factors that influence the local inflammatory environment of the ovary and its surroundings and have the potential to promote existing transcriptional errors and mutations.

Experiment – Interventions, such as tubal ligation that decreases the incidence of ovarian cancer by blocking the exposure route, offers experimental support for this mechanism. The use of cornstarch-based dusting powders as a substitute for talcum powder products offers additional experimental support.

Analogy – Have there been other environmental exposures that have been associated with ovarian cancers that act via similar mechanisms? Talcum powder is somewhat unique in terms of its delivery mechanism. But beyond that, the case of asbestos exposure is similar. Asbestos exposure has resulted in excesses of ovarian cancers in exposed women, although the route of exposure is thought to be by inhalation. Nonetheless, asbestos is a mineral very similar both chemically and structurally to talc that has been found in the ovary and peritoneal cavity of exposed women. The mechanisms of carcinogenesis for both asbestos and talc are similar and analogous. Further, talc-based products contain asbestos and non-asbestos mineral fibers having carcinogenic potential.

When considering these factors, I gave the most weight to the compelling strength of association and consistency, as well as the well-described biologic mechanism.

The currently available scientific research, when considered in its totality, demonstrates a cause and effect relationship between the use of talcum powder products and the development of epithelial ovarian cancer. This opinion is reinforced by my consideration of the Hill factors for the assessment of causation.

In reviewing the scientific and medical literature on talcum powder product use, I also performed a risk assessment and considered whether perineal use of those products poses a safety risk to consumers. This involved careful consideration of the epidemiological literature, data on the dose-response relationship and exposure, as well as the nature of these products, which are used primarily for personal care. I also considered evidence of the toxicity of these products, for which repeated testing and analyses have shown to contain carcinogens.

In considering the weight of this epidemiologic, toxicologic, and mechanistic evidence, across multiple studies, time, demographics, and researchers, demonstrating a consistent association between perineal use of talcum powder products and ovarian cancer, it is my opinion that talcum powder products increase the risk of ovarian cancer and pose a significant health hazard.

In conclusion, it is my opinion that the perineal use of talcum powder products causes ovarian cancer in some users and increases the risk of ovarian cancer in all users of these products.

All of my opinions in this report are provided with respect to a reasonable degree of medical and scientific certainty. I reserve the right to amend or supplement my report as new information becomes available.

References

- Acheson ED, G. M. (1982). Mortality of two groups of women who manufactured gas masks from chrysotile and crocidolite asbestos: a 40-year follow-up. *British Journal of Industrial Medicine*, 39, 344-348.
- American Cancer Society. (n.d.). *Key Statistics for Ovarian Cancer*. Retrieved October 31, 2018, from American Cancer Society: <https://www.cancer.org/cancer/ovarian-cancer/about/key-statistics.html>
- American Cancer Society. (n.d.). *What Is Ovarian Cancer?* Retrieved 10 31, 2018, from American Cancer Society: <https://www.cancer.org/cancer/ovarian-cancer/about/what-is-ovarian-cancer.html>
- Balkwill Fran, M. A. (2001). Inflammation and cancer: back to Virchow? *The Lancet*, 357, 540-545.
- Berge W, e. a. (2017). Genital use of talc and risk of ovarian cancer: a meta-analysis. *European Journal of Cancer Prevention*.
- Berry G, N. M. (2000). Mortality from all cancers of asbestos factory workers in east London 1933-80. *Occupational and Environmental Medicine*, 57, 782-785.
doi:0.1136/oem.57.11.782

- Bertolotti M, F. D. (2008). Mortality in the cohort of the asbestos cement workers in the Eternit plant in Casale Monferrato (Italy). *Epidemiol Prev*, 32, 218-228.
- Blumenkrantz MJ, G. N. (1981). Retrograde menstruation in women undergoing chronic peritoneal dialysis. 57(5), 667-670.
- Booth M, B. V. (1989). Risk factors for ovarian cancer: a case-control study. *British Journal of Cancer*, 60, 592-598.
- Buz'Zard AR, L. B. (2007). Pycnogenol reduces talc-induced neoplastic transformation in human ovarian cell cultures. *Phytotherapy Research*, 21, 579-586.
- Chang C-J, e. a. (2017). Occupational exposure to talc increases the risk of lung cancer: a meta-analysis of occupational cohort studies. *Canadian Respiratory Journal*, 2017(1270608), 1-12. Retrieved from <https://doi.org/10.1155/2017/1270608>
- Chang S, R. H. (1997). Perineal talc exposure and risk of ovarian carcinoma. *Cancer*, 79, 2396-2401.
- Chen Y, W. P. (1992). Risk factors for epithelial ovarian cancer in Beijing, China. *International Journal of Epidemiology*, 21, 23-29.
- Cook LS, e. a. (1997). Erratum in "Perineal powder exposure and the risk of ovarian cancer". *American Journal of Epidemiology*, 148, 410.
- Cook LS, K. M. (1997). Perineal powder exposure and the risk of ovarian cancer. *American Journal of Epidemiology*, 145, 459-465.
- Coussens LM, Z. W. (2002). Inflammation and cancer. *Nature*, 420(6917), 860-867. doi:10.1038/nature01322
- Cramer Daniel W, V. A. (2016). The Association Between Talc Use and Ovarian Cancer: A Retrospective Case-Control Study in Two US States. *Epidemiology*, 27, 334-346.
- Cramer DW, W. W. (1982). Ovarian cancer and talc: A case-control study. *Cancer*, 50, 372-376.
- Egli GE, M. N. (1961). The transport of carbon particles in the human female reproductive tract. *Fertility and Sterility*, 12(2), 151-155.
- Ferrante D, B. M. (2007). Cancer mortality and incidence of mesothelioma in a cohort of wives of asbestos workers in Casale Monferrato. *Environmental Health Perspectives*, 115, 1401-1405.
- Fletcher NM, M. I. (2018). Talcum powder enhances oxidative stress in ovarian cancer cells. *Presented at the 65th meeting of the Society for Reproductive Investigation, San Diego California*.
- Fletcher NM, S. G. (2018). Talcum powder enhances cancer antigen 125 in ovarian cancer cells and normal ovarian epithelial cells. *Presented at the 65th meeting of the Society for Reproductive Investigation, San Diego California*.

- Fox, A. W. (1982). Mortality of female gas mask assemblers. *British Journal of Industrial Medicine*, 39, 34-38.
- Germani D, B. S. (1999). Cohort and mortality study of women compensated for asbestosis in Italy. *American Journal of Industrial Medicine*, 36, 129-134. doi:10.1002/(SICI)1097-0274(199907)36:1<129::AID-AJIM18>3.0.CO;2-9
- Halme J, e. a. (1984). Retrograde menstruation in healthy women and in patients with endometriosis. *Obstetrics and Gynecology*, 64(2), 151-154.
- Harlow BL, C. D. (1992). Perineal exposure to talc and ovarian cancer risk. *Obstetrics and Gynecology*, 80, 19-26.
- Harlow BL, H. P. (1995). A review of perineal talc exposure and risk of ovarian cancer. *Regulatory Toxicology and Pharmacology*, 21, 254-260.
- Harlow BL, W. B. (1989). A case-control study of borderline ovarian tumors: the influence of perineal exposure to talc. *American Journal of Epidemiology*, 130, 390-394.
- Harper, S. (2019). Talc induces a pro-oxidant state in normal and ovarian cancer cells through gene point mutations in key redox enzymes. *pending publication*.
- Hartge P, H. R. (1988). Talc and ovarian cancer [letter]. *JAMA*, 250, 1844.
- Heller DS, W. C. (1996). The relationship between perineal cosmetic talc usage and ovarian talc particle burden. *American Journal of Obstetrics and Gynecology*, 174, 1507-1510.
- Henderson WJ, C. J. (1971). Talc and carcinoma of the ovary and cervix. *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 78, 266-272.
- Henderson WJ, T. H. (1979). Talc in normal and malignant tissue. *The Lancet*, 499.
- Hill, A. (1965). The environment and disease: Association or causation. *Proceedings of the Royal Society of Medicine*, 58(5), 295-300.
- International Agency for Research on Cancer. (2010). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Volume 93 - Carbon Black, Titanium Dioxide, and Talc*. Lyon, Freance.
- International Agency for Research on Cancer. (2012). Arsenic, Metals, Fibres and Dusts, Vol 100C, A review of human carcinogens. In IARC, *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*. Lyon, France: World Health Organization.
- Jaiswal M, L. N. (2000). Inflammatory cytokines induce DNA damage and inhibit DNA repair in cholangiocarcinoma cells by a nitric oxide-dependent mechanism. *Cancer Res*, 60, 184-190.
- Jurinski JB, R. J. (2001). Biodurability of talc. *American Mineralogist*, 86(4), 392-399.

- King, H. M. (n.d.). *Talc: The Softest Mineral*. Retrieved 10 31, 2018, from Geology.com: <https://geology.com/minerals/talc.shtml>
- LA Torre, B. T. (2018). Ovarian Cancer Statistics, 2018. *CA A Cancer Journal for Clinicians*, 68, 284–296.
- Langseth H, H. S. (2008). Perineal use of talc and risk of ovarian cancer. *J Epidemiol Community Health*, 62, 358-360. doi:10.1136/jech.2006.047894
- Lockey, J. (1981). Nonasbestos fibrous minerals. *Clinics in Chest Medicine*, 2(2), 203-218.
- Longo WE, M. R. (2017). *Analysis of Johnson and Johnson Baby Powder and Valiant Shower To Shower Talc Products for Amphibole (Tremolite) Asbestos: Expert Report*. Materials Analytical Services, LLC, Atlanta .
- Magnani C, F. D.-A. (2008). Cancer risk after cessation of asbestos exposure: a cohort study of Italian asbestos cement workers. *Occupational and Environmental Medicine*, 65, 164-170. doi:10.1136/oem.2007.032847
- Mostafa SAM, e. a. (1985). Foreign body granulomas in normal ovaries. *Obstetrics and Gynecology*, 66(5), 701-702.
- Muscat JE, H. M. (2008). Perineal Talc Use and Ovarian Cancer: A Critical Review. *Eur J Cancer Prev.*, 17(2), 139-146. doi:10.1097/CEJ.0b013e32811080ef
- Nadler DL, I. Z. (2014). Estimating Cancer Latency Times Using a Weibull Model. *Advances in Epidemiology*, 2014, 1-8. doi:10.1155/2014/746769
- National Institute for Occupational Safety and Health. (2011). *Asbestos fibers and other elongate mineral particles: State of the science and roadmap for research*. NIOSH Current Intelligence Bulletin No. 62.
- National Toxicology Program. (1993). *Toxicology and Carcinogenesis Studies of Talc (CAS No 14807-96-6)(NonAsbestiform) in F344/N.Rats and B6C3F1 Mice (Inhalation Studies) (1993)*. Washington: USDHHS.
- Ness Roberta B, C. C. (1999). Possible role of ovarian epithelial inflammation in ovarian cancer. *Journal of the National Cancer Institute*, 91, 1459-1467.
- Newhouse ML, B. G. (1972). A study of the mortality of female asbestos workers. *British Journal of Industrial Medicine*, 29, 134-141.
- Okada, F. (2007). Beyond foreign-body-induced carcinogenesis: Impact of reactive oxygen species derived from inflammatory cells in tumorigenic conversion and tumor progression. *International Journal of Cancer*, 121, 2364–2372.
- Paoletti L, S. C. (1984). Evaluation by Electron Microscopy Techniques of Asbestos Contamination in Industrial, Cosmetic, and Pharmaceutical Talcs. *Regulatory Toxicology and Pharmacology*, 4, 222-235.

- Penninkilampi R, E. G. (2018). Perineal Talc Use and Ovarian Cancer: A Systematic Review and Meta-Analysis. *Epidemiology*, 29, 41-49. doi:10.1097/EDE.0000000000000745
- Pira E, P. C. (2005). Cancer mortality in a cohort of asbestos textile workers. *British Journal of Cancer*, 92, 580-586. doi:10.1038/sj.bjc.6602240
- Prat, J. (2015). Abridged Republication of FIGO's Staging Classification for Cancer of the Ovary, Fallopian Tube, and Peritoneum. *Cancer*, 121, 3452-3454.
- Radić I, e. a. (1988). Immunosuppression induced by talc granulomatosis in the rat. *Clin Exp Immunol*, 73, 316-321.
- Reid A, H. J. (2008). The mortality of women exposed environmentally and domestically to blue asbestos at Wittenoom, Western Australia. *Occupational and Environmental Medicine*, 65, 743-749. doi:10.1136/oem.2007.035782
- Reid A, S. A. (2009). Gynecologic and breast cancers in women after exposure to blue asbestos at Wittenoom. *Cancer Epidemiol Biomarkers Prev*, 18, 140-147. doi:10.1158/1055-9965.EPI-08-0746
- Rohl AN, e. a. (1976). Consumer talcums and powders: mineral and chemical characterization. *Journal of Toxicology and Environmental Health*, 2, 255-284.
- Rohl, A. (1974). Asbestos in talc. *Environmental Health Perspectives*, 9, 129-132.
- Rosenblatt KA, S. M. (1992). Mineral fiber exposure and the development of ovarian cancer. *Gynecological Oncology*, 45, 20-25.
- Rösler JA, W. H. (1994). Mortality rates in a female cohort following asbestos exposure in Germany. *Journal of Occupational Medicine*, 36, 889–893.
- Saed Ghassan M, D. M. (2017). Updates of the role of oxidative stress in the pathogenesis of ovarian cancer. *Gynecologic Oncology*, 145, 595-604. doi:http://dx.doi.org/10.1016/j.ygyno.2017.02.033
- Saed GM, D. M. (2017). Updates on the role of oxidative stress in the pathogenesis of ovarian cancer. *Gynecologic Oncology*, 145, 595-602.
- Schildkraut JM, A. S.-S. (2016). Association between Body Powder Use and Ovarian Cancer: The African American Cancer Epidemiology Study (AACES). *Cancer Epidemiology, Biomarkers & Prevention*, 25(10), 1411–1417. doi:10.1158/1055-9965.EPI-15-1281
- Shukla A, e. a. (2009). Alterations in gene expression in human mesothelial cells correlate with mineral pathogenicity. *American Journal of Respiratory Cell and Molecular Biology*, 41, 114-123.
- Sjösten ACE, H. E. (2004). Retrograde migration of glove powder in the human female genital tract. *Human Reproduction*, 19(4), 991-995. doi:10.1093/humrep/deh156

- Soong TR, H. B. (2018). Evidence for lineage continuity between early serous proliferations (ESPs) in the Fallopian tube and disseminated high-grade serous carcinomas. *Journal of Pathology*, 246(3), 344-351. doi:10.1002/path.5145
- Terry KL, e. a. (2013). Genital powder use and risk of ovarian cancer: a pooled analysis of 8,525 cases and 9,859 controls. *Cancer Prevention Research*, 6(8), 811-821.
- Torre LA, B. T. (2018). Ovarian Cancer Statistics, 2018. *CA Cancer J Clin*, 68, 284-296.
- Trabert, B. (2016). Body Powder and Ovarian Cancer Risk—What Is the Role of Recall Bias? *Cancer Epidemiology, Biomarkers and Prevention*, 25(10), 1369-1370.
- Tzonou A, P. A. (1993). Hair dyes, analgesics, tranquilizers and perineal talc application as risk factors for ovarian cancer. *International Journal of Cancer*, 55, 408-410.
- VanGosen BS, L. H. (2004). *A USGS Study of Talc Deposits and Associated Amphibole Asbestos Within Mined Deposits of the Southern Death Valley Region, California*. United States Geological Survey. Retrieved from <https://pubs.usgs.gov/of/2004/1092/>
- VanOrden D, L. R. (2000). *Weight Percent Compositional Analysis of Seven RTV Talc Samples. Analytical Report to R. T. Vanderbilt Company, Inc. 22 November 2000*. Submitted to Public Comments Record – C. W. Jameson, National Toxicology Program, 10th ROC Nominations "Talc (containing asbestiform fibers)". 4 December 2000., National Toxicology Program.
- Venter PF, M. I. (1979). Migration of a particulate radioactive tracer from the vagina to the peritoneal cavity and ovaries. *S Afr Med. J*, 55, 917-919.
- Whittemore AS, W. M. (1988). Personal and environmental characteristics related to epithelial ovarian cancer. II. Exposures to talcum powder, tobacco, alcohol, and coffee. *American Journal of Epidemiology*, 128, 1228-1240.
- Whysner J, M. M. (2000). Perineal application of talc and cornstarch powders: Evaluation of ovarian cancer risk. *Am J Obstet Gynecol*, 182, 720-724.
- Wild, P. (2006). Lung cancer risk and talc not containing asbestiform fibres: a review of the epidemiological evidence. *Occup Environ Med*, 63, 4-9. doi:10.1136/oem.2005.020750
- Woodruff, J. (1979). The pathogenesis of ovarian neoplasias. *The Johns Hopkins Medical Journal*, 144(4), 117-120.

Exhibit A

Curriculum Vitae

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Biosketch

Arch "Chip" Carson, MD, PhD is a physician (The Ohio State University), board certified in Occupational Medicine (American Board of Preventive Medicine), who holds a Doctor of Philosophy degree in Toxicology (University of Cincinnati, Kettering Laboratory). He has served on the faculty of the University of Cincinnati and the New York University Medical Center and joined the faculty of the University of Texas School of Public Health in 1992 in its Environmental Sciences Discipline and Occupational and Environmental Health and Aerospace Medicine Module. He is Associate Professor of Occupational Health, directs the Occupational and Environmental Medicine Residency Program and is a member of the research team of the Southwest Center for Occupational and Environmental Health, a NIOSH Education and Research Center, and WHO Collaborating Centre in Occupational Health. He maintains a clinical practice of occupational medicine and medical toxicology. In his more recent role as Medical Director for the University of Texas Medical Branch in Galveston, he is responsible for the health monitoring and care of more than 15,000 employees. He is a frequent consultant to governments, corporations and the legal community on matters related to industrial chemical exposure, toxicology and environmental justice. His research interests include: environmental and occupational chemical exposures, inhalation injuries, metal exposures and cancer, and professional training in occupational medicine.

Professional Activities/Employment

2017-18	University of Texas Medical Branch, Galveston, Assistant Clinical Professor of Preventive Medicine and Family Medicine
2017-18	University of Texas Medical Branch, Galveston, Medical Director, Employee Health Services.
2017-18	Enbridge Corporation, Houston Texas, Medical Director, Employee Health Services.
2010-18	University of Texas Health Science Center, Houston, Associate Professor of Occupational Health.
2010-18	University of Texas Health Science Center at Houston, Program Director, Occupational and Environmental Medicine Residency.
1991-18	Private practice of Occupational Medicine and Toxicology, New York, Texas and Ohio.
2011-18	Spectra Energy Corporation, Houston Texas, Medical Director, Employee Health Services.
1997-13	Texas Medical Center Inc., Houston Texas, Medical Director, Employee Health Services.
1992-08	University of Texas School of Public Health, Assistant Professor of Occupational Medicine and Environmental Sciences.
1998-08	University of Texas Health Science Center at Houston, Program Director, Occupational and Environmental Medicine Residency.
2003-08	Southwest Center for Occupational and Environmental Health, Principal Investigator and Director, Diller Phosgene Exposure Incident Registry of the American Chemistry Council.

2000-06	Chevron Phillips Chemical Company, Houston Texas, Corporate Medical Director.
2003-05	U.S. Department of Energy Office of Worker Advocacy Physician Review Panel Appointee.
1997-04	Southwest Center for Occupational and Environmental Health, Principal Investigator, City of Houston Lead Poisoning Epidemiology Project.
1992-03	UT Health Services, University of Texas Houston Health Science Center, Attending Physician, Occupational Medicine and Toxicology.
1997-01	University of Houston Downtown, Medical Director, Student Health Service.
1998-99	University of Texas School of Public Health, Convener of the Occupational/Environmental Health and Aerospace Medicine Module.
1992-97	Respiratory Consultants of Houston, PA, Attending Physician, Occupational Medicine and Toxicology.
1992-95	Exxon Chemical Americas, Baytown Polymer Center and Basic Chemicals Technology, Baytown TX, Consultant Physician.
1990-91	New York University Medical Center, Bellevue Hospital, Tisch Hospital, and Manhattan VA Hospital, New York NY, Dept. of Medicine, Clinical Instructor.
1982-90	Chemical Information Services Inc, Cincinnati OH, Associate in Toxicology.
1978-87	University of Cincinnati College of Medicine, Cincinnati OH, Instructor and Lecturer, Adjunct Assistant Professor of Industrial Toxicology.
1974-79	University of Cincinnati College of Medicine, Kettering Laboratory, Cincinnati OH, Research Technologist in Occupational Medicine and Clinical Studies.
1969-74	Millstone Inc., Cincinnati OH, Design Engineer, environmental control systems.

Educational Background

2002	Certificate of Board Eligibility, Medical Toxicology, American Board of Preventive Medicine/American Board of Emergency Medicine
1992	Certificate of Training - Residency in Occupational Medicine University of Texas Health Science Center at Houston, School of Public Health, and Southwest Center for Occupational and Environmental Health, Houston TX, 1992.
1991	Certificate of Training - Postgraduate Internship in Internal Medicine, New York University Medical Center and Bellevue Hospital Center, New York NY.
1990	MD - Ohio State University College of Medicine, Columbus OH.
1987	PhD - Kettering Laboratory, University of Cincinnati College of Medicine, Cincinnati OH, awarded in the field of "Environmental Health – Toxicology."
1973	BS - University of Cincinnati College of Arts and Sciences Cincinnati OH. Awarded in "Biological Sciences with Concentration in Engineering."
1969	Rensselaer Polytechnic Institute, Troy NY. Management Engineering
1968	Villa Madonna College, Covington KY. Certificate in Contemporary Physics.

Fellowships

2011-13	UTHealth, Health Educators Fellowship, University of Texas Health Science Center at Houston.
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- 1983-85 American Lung Association Fellowship in Lung Research (Inhalation Toxicology), American Lung Association of Southwestern Ohio, Grant.
- 1981-82 Owens Corning Fiberglas, Graduate Research Fellowship in Combustion Toxicology.
- 1979-80 National Institute for Occupational Safety and Health, Centers for Disease Control, Doctoral Fellowship in Industrial Toxicology.

Certifications

- 2012 License to practice medicine, State of Ohio 35.098635
- 2010 Certified Healthy Homes Specialist – National Environmental Health Association.
- 2002 Board Eligibility, Medical Toxicology, American Board of Preventive Medicine/American Board of Emergency Medicine.
- 1994 Board Certification, Occupational Medicine, American Board of Preventive Medicine.
- 1992 License to practice medicine, State of Texas J2524.
- 1991 License to practice medicine, State of New York 186563.
- 1982 Emergency Hazard Response, Environmental and Industrial Chemical Accident Management, U.S. Environmental Protection Agency.
- 1979 Pulmonary Function Testing for Occupational Surveillance, NIOSH #003.

Professional Community Service

- 2013-18 University of Texas Health Science Center at Houston, Steering Committee on Interprofessional Collaboration
- 2013-18 University of Texas Health Science Center at Houston, Chemical Safety Committee.
- 1998-18 Association of Environmental and Occupational Clinics/ATSDR community resource on toxic exposures and health consequences, Federal Region VI.
- 1997-18 City of Houston Biological, Chemical and Radiation Emergency Preparedness Program. Medical Toxicology On-Call Advisor to the Houston Medical Strike Team.
- 1998-18 Association of Occupational and Environmental Medicine Residency Directors. Chairman 2005-2006
- 2010-18 University of Texas Health Science Center at Houston, Graduate Medical
1997-08 Education Committee
- 2010-18 University of Texas Health Science Center, Houston, Community/Press
1994-08 Resource and Speaker via Public Information Office, (Toxic Exposures and Environmental Health).
- 1996-18 American College of Occupational and Environmental Medicine, Council on Academic Affairs and Co-chair, Academic Section 2004-2006. Occupational Medicine Residency Directors Committee, Chair 2006-2007, Appointed Member, Taskforce on the Future of Occupational Medicine Education 2005-2007. Appointed Co-chair, Taskforce on the Future of Occupational Medicine Education 2013-2015.
- 1996-18 Texas College of Occupational and Environmental Medicine. Secretary/Treasurer-2004-5, President Elect-2005-6, President-2006-7, Past President 2007-8.
- 2003-12 Boy Scouts of America, Sam Houston Council, Registered Adult Leader and Merit Badge Counselor.
- 2005-08 University of Texas School of Public Health, Practice Council Co-chair

2003-05	U.S. Department of Energy Office of Worker Advocacy Physician Review Panel Appointee.
1996-00	American Public Health Association, Occupational Health Subcommittee
1994-96	Advisory Board, National Environmental Education and Training Center (NEETC), Curriculum Development Committee.
1981-85	Tri-State Air Committee Inc., Cincinnati OH, (voluntary air quality organization) Scientific Advisor, Elected to Board of Directors in 1982, President and Chairman 1984-85.
1981-85	American Lung Association of Southwestern Ohio, Cincinnati OH, (voluntary health organization) speakers bureau.
1982-83	City of Cincinnati, Appointment to Occupational Health Scientific Liaison Board (municipal advisory committee).
1981-83	Cincinnati Area Toxic Substances Coalition, Cincinnati OH, (coalition of business, voluntary, and labor organizations with interest in environmental toxic substance issues) Cofounder and Chairman.
1982-83	Ohio River Valley Committee on Occupational Safety and Health, Cincinnati OH, (organized labor coalition) Scientific Resource Committee.
1972-82	Walnut Hills-Evanston Medical Center, Cincinnati OH, (primary care center) Board of Directors.

Professional Societies

1991-18	American College of Occupational and Environmental Medicine.
1991-18	Texas College of Occupational and Environmental Medicine
2007-18	Texas Public Health Association.
2006-18	International Congress on Occupational Health.
2003-18	American College of Medical Toxicology.
2002-06	Society of Occupational and Environmental Health.
2001-06	American Conference of Governmental Industrial Hygienists.
1994-00	American Public Health Association.
1983-87	American Industrial Hygiene Association.
1983-87	Society of Toxicology.
1980-85	American Thoracic Society, Associate Member and Participant in Occupational and Environment Scientific Session.

Publications

Anderson F, **Carson A**, Whitehead L and Burau K. Age, Race and Gender Spatiotemporal Disparities of COPD Emergency Room Visits in Houston, Texas. Occupational Diseases and Environmental Medicine. 3: 1-9, 2015. <http://dx.doi.org/10.4236/odem.2015.31001>.

Anderson F, **Carson A**, Whitehead L and Burau K. Spatiotemporal Analysis of the Effect of Ozone and Fine Particulate on CVD Emergency Room Visits in Harris County, Texas. Open Journal of Air Pollution, 3: 87-99, 2014. <http://dx.doi.org/10.4236/ojap.2014.34009>.

- Calcote, JC, **Carson, A**, Peskin, MF, Emery, RJ. An assessment of post-disaster psychological stress in hazardous waste operations and emergency response (HAZWOPER) workers. *Disaster Med Public Health Preparedness*. 7:452-460, 2013. PMID 24274124.
- Delclos GL, Tullis LA, **Carson A**. The services industry. In *Occupational and Environmental Lung Diseases*. Tarlo SM, Cullinan, Nemery B eds. 2010 pp.258-271. Wiley-Blackwell, West Sussex, UK.
- Pugach S, Clarkson T, (**Carson A**). Prenatal mercury exposure and postnatal outcome: clinical case report and analysis. *Clin Toxicol* 47:366-370, 2009.
- Pauluhn J, **Carson A**, Costa DL, Gordon T, Kodavanti U, Last JA, Matthay MA, Pinkerton KE and Sciuto AM. Workshop summary: phosgene-induced pulmonary toxicity revisited: appraisal of early and late markers of pulmonary injury from animal models with emphasis on human significance. *Inhalation Toxicology*. 19(10):789-810, 2007.
- Delclos GL, Gimeno D, Arif AA, Burau KD, **Carson A**, Lusk C, Stock T, Symanski E, Whitehead LW, Zock JP, Benavides FG and Anto JM. Occupational risk factors and asthma among health care professionals, *American Journal of Respiratory & Critical Care Medicine*. 175(7):667-75, 2007.
- Savely SM, **Carson A** and Delclos GL. "A survey of the implementation status of environmental management systems in U.S. colleges and universities" *J Cleaner Production*, 15(7) 650-659, 2007.
- Savely SM, **Carson A** and Delclos GL. "An environmental management system implementation model for U.S. colleges and universities" *J Cleaner Production*, 15(7) 660-670, 2007.
- Delclos GL, Arif AA, Aday L, **Carson A**, Lai D, Lusk C, Stock T, Symanski E, Whitehead LW, Benavides FG and Anto JM. Validation of an asthma questionnaire for use in healthcare workers. *Occupational & Environmental Medicine*. 63(3):173-9, 2006.
- Delclos GL, Bright KA, **Carson A**, Felknor SA, Mackey TA, Morandi MT, Schulze LJH and Whitehead LW. "A global survey of occupational health competencies and curriculum" *International Journal of Occupational and Environmental Health*; 11:181-194, 2005.
- Nooka A, Duonghi L, **Carson A**, Hassan M. Assessing Occupational Risk for Pancreatic Cancer by Chemical Exposures and Work History: A Case-Control study at MD Anderson Cancer Center. American Association for Cancer Research, Orlando. March, 2004.
- Mitchell CS, Moline J, Avery AN, Baker D, Blessman JE, **Carson A**, Cosby O, Darcey D, Ducatman A, Emmett EA, Forst L, Gerr F, Gochfeld M, Guidotti TL, Harber P, Hu H, Hegmann KT, Kipen HM, Levin J, McGrail MP, Meyer JD, Mueller KL, Prince S, Rubin R, Schwerha JJ, Sprince NL, Taiwo O and Upfal M. In response to the 2002, vol. 22, no. 4 article entitled "The rise and fall of occupational medicine in the United States" [Letter] *Am J Preventive Med*. 23(4):307-9, 2002.
- Carson A** and Delclos GL. "The Respiratory System," in *Modern Industrial Hygiene: Volume II – Biological Aspects*, JL Perkins, ed. 2003, American Conference of Governmental Industrial Hygienists, Cincinnati.
- Carson A**, Colombo S and Alavi. A, City of Houston Childhood Lead Poisoning Prevention Program: Case Density and Impact Analysis, March 31, 2000, Technical Report (Principal Investigator).
- Townsend MC, Lockett JE, Velez H, **Carson A**, Cowl CT, Delclos GL, Gerstenhaber BJ, Harber PI, Horvath EP, Jolly AT, Jones SH, Knackmuhs GG, Lindesmith LA, Markham TN, Raymond LW, Rosenberg DM, Sherson D, Smith DD, and Wintermeyer SF. ACOEM Position Statement – "Spirometry in the Occupational Setting" *JOEM*; 42: 228-245, 2000.
- Bright K, Delclos G, **Carson A**, Felknor S, Mackey T, Morandi M, Schultz L and Whitehead L. A Global Study of Occupational Health Competencies and Curricula, Report to the World Health Organization, March, 2000, Southwest Center for Occupational and Environmental Health.

Carson A, Guevara E, Delclos GL, Murray KA, Burau KD, Morandi MT, Felknor SA, ("A Study of General Health of Workers of the Industrial Complex of Barrancabermeja") in [Compendium on Occupational Health in the Petroleum Industry of Colombia: Technical and Scientific Report of the "Occupational Health in the Petroleum Industry" Project], 1999 Pan American Health Organization (co-author).

Carson A, Hangoc V and Bahrainwala M, City of Houston Childhood Lead Poisoning Prevention Program: Case Density and Impact Analysis, June 30, 1999, Technical Report (Principal Investigator).

Carson A, Spears B, and Burau K, City of Houston Childhood Lead Poisoning Prevention Program: Case Density and Impact Analysis, June 30, 1998, Technical Report (Principal Investigator).

Carson A, Detry M, Spears B, and Burau K, City of Houston Childhood Lead Poisoning Prevention Program: Case Density and Impact Analysis, June 30, 1997, Technical Report (Principal Investigator).

Delclos GL and **Carson A**, "Acute Gaseous Exposures," in Occupational and Environmental Respiratory Diseases, P Harber, M Schenker, and J Balmes eds. 1995, Mosby Yearbook Pub., St. Louis.

Carson A, "Respiratory Effects of Exposure to Fresh Smokes from Pyrolytic Decomposition of Styrene Plastic in Rats." Doctoral Dissertation, University of Cincinnati Kettering Laboratory, 1987.

Carson A, "A Dynamic Method for the Generation of Fresh Smokes From Combustion or Pyrolytic Decomposition of Structural Materials." Doctoral Dissertation, University of Cincinnati Kettering Laboratory, 1987.

Samuels SJ, Lemasters GK and **Carson A**, "Statistical Methods for Describing Occupational Exposure Measurements," Am. Ind. Hyg. Assoc. J., 46:427-433, 1985.

Lemasters GK, **Carson A** and Samuels SJ, "Occupational Styrene Exposure for Twelve Product Categories in the Reinforced-Plastics Industry," Am. Ind. Hyg. Assoc. J., 46:434-441, 1985.

Lockey JE, Brooks SM, Jarabek AM, Khoury PR, McKay RT, **Carson A**, Morrison JA, Wiot JF and Spitz HB. "Pulmonary changes after exposure to vermiculite contaminated with fibrous tremolite" Am Rev Respir Dis. 129(6):952-8, 1984.

Lockey JE, Jarabek A, **Carson A**, McKay R, Harber P, Khoury P, Morrison J, Wiot J, Spitz H and Brooks SM, "Pulmonary Hazards from Vermiculite," in Health Issues Related to Metal and Nonmetallic Mining, WL Wagner, W Rom and P Merchant eds. 1983, Butterworth's, Boston.

Vinegar A and **Carson A**, "Pulmonary Function Changes in Chinese Hamsters Exposed Six Months to Diesel Exhaust," Environ Int, 5:369-371, 1981.

Lockey JE, Jarabek A, **Carson A**, McKay R, Harber P, Khoury P, Morrison J, Prior J and Brooks SM, "Health Effects of Vermiculite Exposure," Am Rev Respir Dis, 123:133, 1981 abstract.

Lockey JE, Jarabek A, **Carson A**, McKay R, Harber P, Khoury P, Morrison J and Brooks SM, "Single-Breath Diffusing Capacity (DLCOsb) in a Working Population," Am Rev Respir Dis, 123:132, 1981 abstract.

Vinegar A, **Carson A** and Pepelko WE, "Pulmonary Function Changes in Chinese Hamsters Exposed to Diesel Exhaust," in Health Effects of Diesel Engine Emissions, Vol. 2, WE Pepelko, RM Danner and NA Clarke eds, 1980, US Environmental Protection Agency, Washington.

Carson A, Vinegar A, Leng J and Cooper G, "Effects of Chronic Exposure to some Diesel Exhaust Components on Lung Function in Rats," Fed Proc, 39:1091, 1980 abstract.

Elia VJ, Anderson LA, MacDonald TJ, **Carson A**, Buncher CR and Brooks SM, "Determination of Urinary Mandelic and Phenylglyoxylic Acids in Styrene Exposed Workers and a Control Population," Am Ind Hyg Assoc J, 41:922-926, 1980.

Brooks SM, Anderson LA, Emmett E, **Carson A**, Tsay JY, Elia VJ, Buncher CR and Karbowsky R, "The Effects of Protective Equipment on Styrene Exposure in Workers in the Reinforced Plastics Industry," Arch Environ Health, 35:287-294, 1980.

Brooks SM, Zipp T, Barber M and **Carson A**, "Measurement of Maximal Expiratory Flow Rates in Cigarette Smokers Using Gases of High and Low Densities," Am Rev Respir Dis, 118:75-81, 1978.

Exhibit B

LITERATURE:

- “A Survey of the Long-Term Effects of Talc and Kaolin Pleurodesis.” *British Journal of Diseases of the Chest* 73 (1979): 285–88.
- Acencio, Milena M. P., Evaldo Marchi, Lisete R. Teixeira, Bruna Rocha Silva, Juliana Sanchez Silva, Carlos Sergio Rocha Silva, Vanessa Adelia Alvarenga, Leila Antonangelo, Francisco Suso Vargas, and Vera Luiza Capelozzi. “Talc Particles and Pleural Mesothelium Interface Modulate Apoptosis and Inflammation.” *Pathology* 46, no. S2 (2014): S76.
- ACGIH. Product: Asbestos: TLV(R) Chemical Substances 7th Edition Documentation. Accessed August 16, 2018.
- ACGIH. 2017 TLVs and BEIs: ACGIH. Accessed August 16, 2018.
- Acheson, E D, M J Gardner, E C Pippard, and L P Grime. “Mortality of Two Groups of Women Who Manufactured Gas Masks from Chrysotile and Crocidolite Asbestos: A 40-Year Follow-Up.” *British Journal of Industrial Medicine* 39, no. 4 (November 1982): 344–48.
- Akhtar, Mohd Javed, Maqsood Ahamed, M.A. Majeed Khan, Salman A. Alrokayan, Iqbal Ahmad, and Sudhir Kumar. “Cytotoxicity and Apoptosis Induction by Nanoscale Talc Particles from Two Different Geographical Regions in Human Lung Epithelial Cells.” *Environmental Toxicology* 29 (2014): 394–406.
- Akhtar, Mohd Javed, Sudhir Kumar, Ramesh Chandra Murthy, Mohd Ashquin, Mohd Imran Khan, Govil Patil, and Iqbal Ahmad. “The Primary Role of Iron-Mediated Lipid Peroxidation in the Differential Cytotoxicity Caused by Two Varieties of Talc Nanoparticles on A549 Cells and Lipid Peroxidation Inhibitory Effect Exerted by Ascorbic Acid.” *Toxicology in Vitro: An International Journal Published in Association with BIBRA* 24, no. 4 (June 2010): 1139–47.
- American Cancer Society. “Key Statistics for Ovarian Cancer.”
- American Cancer Society. “What Is Ovarian Cancer?,”
- Anderson, Garnet L., Howard L. Judd, Andrew M. Kaunitz, David H. Barad, Shirley A. A. Beresford, Mary Pettinger, James Liu, S. Gene McNeeley, Ana Maria Lopez, and Women’s Health Initiative Investigators. “Effects of Estrogen plus Progestin on Gynecologic Cancers and Associated Diagnostic Procedures: The Women’s Health Initiative Randomized Trial.” *JAMA* 290, no. 13 (October 1, 2003): 1739–48.
- Antoniou, A., P. D. P. Pharoah, S. Narod, H. A. Risch, J. E. Eyfjord, J. L. Hopper, N. Loman, et al. “Average Risks of Breast and Ovarian Cancer Associated with BRCA1 or BRCA2 Mutations Detected in Case Series Unselected for Family History: A Combined Analysis of 22 Studies.” *American Journal of Human Genetics* 72, no. 5 (May 2003): 1117–30.
- Arellano-Orden, Elena, Auxiliadora Romero-Falcon, Jose Martin Juan, Manuel Ocana Jurado, Francisco Rodriguez-Panadero, and Ana Montes-Worboys. “Small Particle-Size Talc Is Associated with Poor Outcome and Increased Inflammation in Thoracoscopic Pleurodesis.” *Respiration* 86 (2013): 201–9.
- Armstrong, Deborah K., Brian Bundy, Lari Wenzel, Helen Q. Huang, Rebecca Baergen, Shashikant Lele, Larry J. Copeland, Joan L. Walker, Robert A. Burger, and Gynecologic Oncology Group. “Intraperitoneal Cisplatin and Paclitaxel in Ovarian Cancer.” *The New England Journal of Medicine* 354, no. 1 (January 5, 2006): 34–43.
- “ATSDR - Toxicological Profile: Asbestos.” Accessed August 16, 2018.
- Baldwin, Lauren A., Bin Huang, Rachel W. Miller, Thomas Tucker, Scott T. Goodrich, Iwona

- Podzielinski, Christopher P. DeSimone, Fred R. Ueland, John R. van Nagell, and Leigh G. Seamon. "Ten-Year Relative Survival for Epithelial Ovarian Cancer." *Obstetrics & Gynecology* 120, no. 3 (September 2012): 612–18.
- Balkwill, Fran, and Alberto Mantovani. "Inflammation and Cancer: Back to Virchow?" *The Lancet* 357, no. 9255 (February 2001): 539–45.
- Bartrip, P.W. "History of Asbestos Related Disease." *Postgrad Med J* 80 (2004): 72–76.
- Beck, B. D., H. A. Feldman, J. D. Brain, T. J. Smith, M. Hallock, and B. Gerson. "The Pulmonary Toxicity of Talc and Granite Dust as Estimated from an in Vivo Hamster Bioassay." *Toxicology and Applied Pharmacology* 87, no. 2 (February 1987): 222–34.
- Begg, Melissa D., and Dana March. "Cause and Association: Missing the Forest for the Trees." *American Journal of Public Health* 108, no. 5 (May 2018): 620.
- Belotte, Jimmy, Nicole M. Fletcher, Awoniyi O. Awonuga, Mitchell Alexis, Husam M. Abu-Soud, Ghassan M. Saed, Michael P. Diamond, and Mohammed G. Saed. "The Role of Oxidative Stress in the Development of Cisplatin Resistance in Epithelial Ovarian Cancer." *Reproductive Sciences* 21, no. 4 (2014): 503–8.
- Belotte, Jimmy, Nicole M. Fletcher, Mohammed G. Saed, Mohammed S. Abusamaan, Gregory Dyson, Michael P. Diamond, and Ghassan M. Saed. "A Single Nucleotide Polymorphism in Catalase Is Strongly Associated with Ovarian Cancer Survival." *PloS One* 10, no. 8 (2015).
- Berge, Wera, Kenneth Mundt, Hung Luu, and Paolo Boffetta. "Genital Use of Talc and Risk of Ovarian Cancer: A Meta-Analysis." *European Journal of Cancer Prevention*, January 2017, 1.
- Berge. "Genital Use of Talc and Risk of Ovarian Cancer: A Meta-Analysis." *European Journal of Cancer Prevention: The Official Journal of the European Cancer Prevention Organisation (ECP)* 27, no. 3 (2018): 248–57.
- Berry, G., M. L. Newhouse, and J. C. Wagner. "Mortality from All Cancers of Asbestos Factory Workers in East London 1933-80." *Occupational and Environmental Medicine* 57, no. 11 (November 2000): 782–85.
- Bertolotti, Marinella, Daniela Ferrante, Dario Mirabelli, Mario Botta, Marinella Nonnato, Annalisa Todesco, Benedetto Terracini, and Corrado Magnani. "[Mortality in the cohort of the asbestos cement workers in the Eternit plant in Casale Monferrato (Italy)]." *Epidemiologia E Prevenzione* 32, no. 4–5 (October 2008): 218–28.
- Blank, M M, N Wentzensen, M A Murphy, A Hollenbeck, and Y Park. "Dietary Fat Intake and Risk of Ovarian Cancer in the NIH-AARP Diet and Health Study." *British Journal of Cancer* 106, no. 3 (January 31, 2012): 596–602.
- Blejer, H. and Robert Arlon. "Talc: A Possible Occupational and Environmental Carcinogen." *Journal of Occupational Medicine* No. 15(2) (February 1973): 92-97.
- Blount, A M. "Amphibole Content of Cosmetic and Pharmaceutical Talcs." *Environmental Health Perspectives* 94 (August 1991): 225–30.
- Blumel, Piza, and Zischka-Konorsa, W. "Animal experimental investigations of tissue reactions to starch and talcum powder after intraperitoneal application." *Wiener klinische Wochenschrift* 74, no. 1 (January 1962).
- Blumenkrantz, M. J., N. Gallagher, R. A. Bashore, and H. Tenckhoff. "Retrograde Menstruation in Women Undergoing Chronic Peritoneal Dialysis." *Obstetrics and Gynecology* 57, no. 5 (May 1981): 667–70.
- Boorman, G. A., and J. C. Seely. "The Lack of an Ovarian Effect of Lifetime Talc Exposure in

- F344/N Rats and B6C3F1 Mice.” *Regulatory Toxicology and Pharmacology: RTP* 21, no. 2 (April 1995): 242–43.
- Booth, M., V. Beral, and P. Smith. “Risk Factors for Ovarian Cancer: A Case-Control Study.” *British Journal of Cancer* 60, no. 4 (October 1989): 592–98.
- Bottazzi, Barbara, Elio Riboli, and Alberto Mantovani. “Aging, Inflammation and Cancer.” *Seminars in Immunology*, November 5, 2018.
- Brand, K.G., Lance C. Buoen, Kenneth H. Johnson, and Inge Brand. “Etiological Factors, Stages, and the Role of the Foreign Body in Foreign Body Tumorigenesis: A Review.” *Cancer Research* No. 35 (February 1975): 279-286.
- Brand, K.G. “Cancer Associated with Asbestosis, Schistosomiasis, Foreign Bodies, and Scars.” *Cancer: A Comprehensive Treatise* 2nd Edition. Etiology: Chemical and Physical Carcinogenesis. Plenum Press. (1982).
- Brand, K.G. “Solid State Carcinogenesis.” *Barbury Report 25: Nongenotoxic Mechanisms in Carcinogenesis*. (1987).
- Brodeur, Paul. “The Magic Mineral.” *The New Yorker* October 12, 1968.
- Bunderson-Schelvan, Melisa, Jean C. Pfau, Robert Crouch, and Andrij Holian. “Nonpulmonary Outcomes of Asbestos Exposure.” *Journal of Toxicology and Environmental Health. Part B, Critical Reviews* 14, no. 1–4 (2011): 122–52.
- Burn, John, Anne-Marie Gerdes, Finlay Macrae, Jukka-Pekka Mecklin, Gabriela Moeslein, Sylviane Olschwang, Diane Eccles, et al. “Long-Term Effect of Aspirin on Cancer Risk in Carriers of Hereditary Colorectal Cancer: An Analysis from the CAPP2 Randomised Controlled Trial.” *Lancet (London, England)* 378, no. 9809 (December 17, 2011): 2081–87.
- Butterworth, B.E., J.A.A Popp, R.B. Connolly and T.L. Goldsworthy. “Chemically Induced Cell Proliferation in Carcinogenesis.” *Mechanisms of Carcinogenesis in Risk Identification*. (1992): 279-305.
- Buz’Zard, Amber R., and Benjamin H. S. Lau. “Pycnogenol® Reduces Talc-Induced Neoplastic Transformation in Human Ovarian Cell Cultures.” *Phytotherapy Research* 21, no. 6 (June 2007): 579–86.
- Caldwell, Carlyle G., White Thomas Aubrey, William L. George, and James J. Eberl. Medical dusting powder. United States US2626257A, filed May 21, 1952, and issued January 20, 1953.
- Camargo, M. Constanza, Leslie T. Stayner, Kurt Straif, Margarita Reina, Umaima Al-Alem, Paul A. Demers, and Philip J. Landrigan. “Occupational Exposure to Asbestos and Ovarian Cancer: A Meta-Analysis.” *Environmental Health Perspectives* 119, no. 9 (September 2011): 1211–17.
- Carr, C.J. “Talc: Consumer Uses and Health Perspectives” 21 (1995): 211–15.
- Chan, Andrew T., Edward L. Giovannucci, Jeffrey A. Meyerhardt, Eva S. Schernhammer, Gary C. Curhan, and Charles S. Fuchs. “Long-Term Use of Aspirin and Nonsteroidal Anti-Inflammatory Drugs and Risk of Colorectal Cancer.” *JAMA* 294, no. 8 (August 24, 2005): 914–23.
- Chang, Che-Jui, Yu-Kang Tu, Pau-Chung Chen, and Hsiao-Yu Yang. “Occupational Exposure to Talc Increases the Risk of Lung Cancer: A Meta-Analysis of Occupational Cohort Studies.” *Canadian Respiratory Journal*, 2017.
- Chang, Stella, and Harvey A. Risch. “Perineal Talc Exposure and Risk of Ovarian Carcinoma.” *Cancer* 79, no. 12 (June 15, 1997): 2396–2401.

- Chen, F., K. Gaitskell, M. J. Garcia, A. Albukhari, J. Tsaltas, and A. A. Ahmed. "Serous Tubal Intraepithelial Carcinomas Associated with High-Grade Serous Ovarian Carcinomas: A Systematic Review." *BJOG: An International Journal of Obstetrics and Gynaecology* 124, no. 6 (May 2017): 872–78.
- Chen, Lee-May, and Jonathan S Berek. "Overview of Epithelial Carcinoma of the Ovary, Fallopian Tube, and Peritoneum." *UpToDate*, 2018.
- Chen, L-M, et al. "Epithelial Carcinoma of the Ovary, Fallopian Tube, and Peritoneum: Epidemiology and Risk Factors - UpToDate," 2018.
- Chen, Xi, Gerd A. Müller, Marianne Quaas, Martin Fischer, Namshik Han, Benjamin Stutchbury, Andrew D. Sharrocks, and Kurt Engeland. "The Forkhead Transcription Factor FOXM1 Controls Cell Cycle-Dependent Gene Expression through an Atypical Chromatin Binding Mechanism." *Molecular and Cellular Biology* 33, no. 2 (January 2013): 227–36.
- Chen, Y., P. C. Wu, J. H. Lang, W. J. Ge, P. Hartge, and L. A. Brinton. "Risk Factors for Epithelial Ovarian Cancer in Beijing, China." *International Journal of Epidemiology* 21, no. 1 (February 1992): 23–29.
- Chien, Jeremy, Hugues Sicotte, Jian-Bing Fan, Sean Humphray, Julie M. Cunningham, Kimberly R. Kalli, Ann L. Oberg, et al. "TP53 Mutations, Tetraploidy and Homologous Recombination Repair Defects in Early Stage High-Grade Serous Ovarian Cancer." *Nucleic Acids Research* 43, no. 14 (August 18, 2015): 6945–58.
- Chittenden, B. G., G. Fullerton, A. Maheshwari, and S. Bhattacharya. "Polycystic Ovary Syndrome and the Risk of Gynaecological Cancer: A Systematic Review." *Reproductive Biomedicine Online* 19, no. 3 (September 2009): 398–405.
- Cibula, D., M. Widschwendter, O. Májek, and L. Dusek. "Tubal Ligation and the Risk of Ovarian Cancer: Review and Meta-Analysis." *Human Reproduction Update* 17, no. 1 (January 1, 2011): 55–67.
- Cibula, David, Martin Widschwendter, Michael Zikan, and Ladislav Dusek. "Underlying Mechanisms of Ovarian Cancer Risk Reduction after Tubal Ligation." *Acta Obstetrica Et Gynecologica Scandinavica* 90, no. 6 (June 2011): 559–63.
- CIMBA, Georgia Chenevix-Trench, Roger L Milne, Antonis C Antoniou, Fergus J Couch, Douglas F Easton, and David E Goldgar. "An International Initiative to Identify Genetic Modifiers of Cancer Risk in BRCA1 and BRCA2 Mutation Carriers: The Consortium of Investigators of Modifiers of BRCA1 and BRCA2 (CIMBA)." *Breast Cancer Research* 9, no. 2 (December 2007).
- Cohen, Samuel M., and Lora L. Arnold. "Chemical Carcinogenesis." *Toxicological Sciences* 120, no. suppl_1 (March 1, 2011): S76–92.
- Colditz, Graham A. "Cancer Prevention." *UpToDate*, 2018.
- Collaborative Group on Epidemiological Studies of Ovarian Cancer, V. Beral, R. Doll, C. Hermon, R. Peto, and G. Reeves. "Ovarian Cancer and Oral Contraceptives: Collaborative Reanalysis of Data from 45 Epidemiological Studies Including 23,257 Women with Ovarian Cancer and 87,303 Controls." *Lancet* 371, no. 9609 (January 26, 2008): 303–14.
- Collaborative Group On Epidemiological Studies Of Ovarian Cancer, V. Beral, K. Gaitskell, C. Hermon, K. Moser, G. Reeves, and R. Peto. "Menopausal Hormone Use and Ovarian Cancer Risk: Individual Participant Meta-Analysis of 52 Epidemiological Studies." *Lancet (London, England)* 385, no. 9980 (May 9, 2015): 1835–42.

- Committee on Practice Bulletins—Gynecology, Committee on Genetics, Society of Gynecologic Oncology. “Practice Bulletin No 182: Hereditary Breast and Ovarian Cancer Syndrome.” *Obstetrics and Gynecology* 130, no. 3 (2017): e110–26.
- Compton, Sarah A., Sezgin Ozgür, and Jack D. Griffith. “Ring-Shaped Rad51 Paralog Protein Complexes Bind Holliday Junctions and Replication Forks as Visualized by Electron Microscopy.” *The Journal of Biological Chemistry* 285, no. 18 (April 30, 2010): 13349–56.
- Cook, Linda S., Mary L. Kamb, and Noel S. Weiss. “Perineal Powder Exposure and the Risk of Ovarian Cancer.” *American Journal of Epidemiology* 145, no. 5 (March 1, 1997): 459–65.
- Cook, LS. “Erratum in ‘Perineal Powder Exposure and the Risk of Ovarian Cancer’.” *American Journal of Epidemiology* 148, no. 410 (1997).
- Coussens, Lisa M., and Zena Werb. “Inflammation and Cancer.” *Nature* 420, no. 6917 (December 19, 2002): 860–67.
- Cralley, L. J., M. M. Key, D. H. Groth, W. S. Lainhart, and R. M. Ligo. “Fibrous and Mineral Content of Cosmetic Talcum Products.” *American Industrial Hygiene Association Journal* 29, no. 4 (August 1968): 350–54.
- Cramer, D. W. “Perineal Talc Exposure and Subsequent Epithelial Ovarian Cancer: A Case-Control Study.” *Obstetrics and Gynecology* 94, no. 1 (July 1999): 160–61.
- Cramer, D. W., R. F. Liberman, L. Titus-Ernstoff, W. R. Welch, E. R. Greenberg, J. A. Baron, and B. L. Harlow. “Genital Talc Exposure and Risk of Ovarian Cancer.” *International Journal of Cancer. Journal International Du Cancer* 81, no. 3 (May 5, 1999): 351–56.
- Cramer, D. W., W. R. Welch, R. E. Scully, and C. A. Wojciechowski. “Ovarian Cancer and Talc: A Case-Control Study.” *Cancer* 50, no. 2 (July 15, 1982): 372–76.
- Cramer, Daniel W., Linda Titus-Ernstoff, John R. McKolanis, William R. Welch, Allison F. Vitonis, Ross S. Berkowitz, and Olivera J. Finn. “Conditions Associated with Antibodies Against the Tumor-Associated Antigen MUC1 and Their Relationship to Risk for Ovarian Cancer.” *Cancer Epidemiology Biomarkers & Prevention* 14, no. 5 (May 1, 2005): 1125–31.
- Cramer, Daniel W., Allison F. Vitonis, Kathryn L. Terry, William R. Welch, and Linda J. Titus. “The Association between Talc Use and Ovarian Cancer: A Retrospective Case-Control Study in Two US States.” *Epidemiology (Cambridge, Mass.)*, December 17, 2015.
- Cramer, Daniel, et al. “The Association Between Talc Use and Ovarian Cancer: A Retrospective Case-Control Study in Two US States.” *Epidemiology (Cambridge, Mass.)* 27, no. 3 (May 2016): 334–46.
- Cramer, Daniel W., William R. Welch, Ross S. Berkowitz, and John J. Godleski. “Presence of Talc in Pelvic Lymph Nodes of a Woman with Ovarian Cancer and Long-Term Genital Exposure to Cosmetic Talc.” *Obstetrics and Gynecology* 110, no. 2 Pt 2 (August 2007): 498–501.
- Cramer, Daniel W., William R. Welch, Robert E. Scully, and Carol A. Wojciechowski. “Ovarian Cancer and Talc. A Case-Control Study.” *Cancer* 50, no. 2 (July 15, 1982): 372–76.
- Crum, Christopher P, Jonathan Bijron, and Brooke E. Howitt. “Pathogenesis of Ovarian, Fallopian Tubal, and Peritoneal Serous Carcinomas.” *UpToDate*, 2018.
- Crusz, Shanthini M., and Frances R Balkwill. “Inflammation and Cancer: Advances and New Agents.” *Nature Reviews Clinical Oncology* 12 (October 2015): 584–96.
- Curtis D. Klaassen, and John Doull. *Casarett and Doull’s Toxicology : The Basic Science of*

- Poisons*. 8th Edition. McGraw-Hill Education, 2013.
- Danforth, Kim N., Shelley S. Tworoger, Jonathan L. Hecht, Bernard A. Rosner, Graham A. Colditz, and Susan E. Hankinson. "Breastfeeding and Risk of Ovarian Cancer in Two Prospective Cohorts." *Cancer Causes & Control: CCC* 18, no. 5 (June 2007): 517–23.
- Demirer, Ersin, Christian F. Ghattas, Mohamed O. Radwan, and Elamin M. Elamin. "Clinical and Prognostic Features of Erionite-Induced Malignant Mesothelioma." *Yonsei Med J* 56(2) (2015): 311–323.
- Devaja, Omer. *Ovarian Cancer From Pathogenesis to Treatment*. IntechOpen, 2018.
- Ding, Yuan C., Lesley McGuffog, Sue Healey, Eitan Friedman, Yael Laitman, Shani-Paluch-Shimon, Bella Kaufman, et al. "A Nonsynonymous Polymorphism in IRS1 Modifies Risk of Developing Breast and Ovarian Cancers in BRCA1 and Ovarian Cancer in BRCA2 Mutation Carriers." *Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology* 21, no. 8 (August 2012): 1362–70.
- Dixon, Suzanne C., Christina M. Nagle, Nicolas Wentzensen, Britton Trabert, Alicia Beeghly-Fadiel, Joellen M. Schildkraut, Kirsten B. Moysich, et al. "Use of Common Analgesic Medications and Ovarian Cancer Survival: Results from a Pooled Analysis in the Ovarian Cancer Association Consortium." *British Journal of Cancer* 116, no. 9 (April 25, 2017): 1223–28. <https://doi.org/10.1038/bjc.2017.68>.
- Dodson, R. F., M. O'Sullivan, C. J. Corn, and S. P. Hammar. "Quantitative Comparison of Asbestos and Talc Bodies in an Individual with Mixed Exposure." *American Journal of Industrial Medicine* 27, no. 2 (February 1995): 207–15.
- Donaldson, Ken. "The Inhalation Toxicology of *p*-aramid Fibrils." *Critical Reviews in Toxicology*, No. 39(6) (2009): 487–500.
- Donaldson, Ken, Fiona A. Murphy, Rodger Duffin, Craig A. Poland. "Asbestos, Carbon Nanotubes and the Pleural Mesothelium: A Review of the Hypothesis Regarding the Role of Long Fibre Retention in the Parietal Pleura, Inflammation and Mesothelioma." *Particle and Fibre Toxicology* No. 7 (2010): 5.
- D.R. Petterson. "JNJ 000251888," April 26, 1973.
- Dubeau, L., and R. Drapkin. "Coming into Focus: The Nonovarian Origins of Ovarian Cancer." *Annals of Oncology: Official Journal of the European Society for Medical Oncology* 24 Suppl 8 (November 2013): viii28–35. <https://doi.org/10.1093/annonc/mdt308>.
- Eberl, J. J., and W. L. George. "Comparative Evaluation of the Effects of Talcum and a New Absorbable Substitute on Surgical Gloves." *American Journal of Surgery* 75, no. 3 (March 1948): 493–97.
- Egli, G. E., and M. Newton. "The Transport of Carbon Particles in the Human Female Reproductive Tract." *Fertility and Sterility* 12 (April 1961): 151–55.
- Eng, Kevin H., J. Brian Szender, John Lewis Etter, Jasmine Kaur, Samantha Poblete, Ruea-Yea Huang, Qianqian Zhu, et al. "Paternal Lineage Early Onset Hereditary Ovarian Cancers: A Familial Ovarian Cancer Registry Study." *PLoS Genetics* 14, no. 2 (February 2018): e1007194. <https://doi.org/10.1371/journal.pgen.1007194>.
- "Expert Report of Michael Crowley, Ph.D., In Re: Talcum Powder Prod. Liab. Litig., MDL No. 2738," November 12, 2018.
- Fasching, Peter A., Simon Gayther, Leigh Pearce, Joellen M. Schildkraut, Ellen Goode, Falk Thiel, Georgia Chenevix-Trench, et al. "Role of Genetic Polymorphisms and Ovarian Cancer Susceptibility." *Molecular Oncology* 3, no. 2 (April 2009): 171–81.

- <https://doi.org/10.1016/j.molonc.2009.01.008>.
- Fathalla, M. F. "Incessant Ovulation and Ovarian Cancer - a Hypothesis Re-Visited." *Facts, Views & Vision in ObGyn* 5, no. 4 (2013): 292–97.
- Fathalla, M. F. "Incessant Ovulation--a Factor in Ovarian Neoplasia?" *Lancet* 2, no. 7716 (July 17, 1971): 163.
- FDA. "Ltr to Samuel S. Epstein, M.D., RE: Docket Numbers 94P-0420 and FDA-2008-P-0309-0001 /CP," April 1, 2017.
- Fedak, Kristen M., Autumn Bernal, Zachary A. Capshaw, and Sherilyn Gross. "Applying the Bradford Hill Criteria in the 21st Century: How Data Integration Has Changed Causal Inference in Molecular Epidemiology." *Emerging Themes in Epidemiology* 12, no. 14 (2015).
- "Federal Register Vol. 81, No.243, December 19, 2016 FDA Ban on Surgical Gloves." Accessed August 16, 2018.
- Ferguson, Lynnette R. "Chronic Inflammation and Mutagenesis." *Mutation Research* 690, no. 1–2 (August 7, 2010): 3–11.
- Fernandes, José Veríssimo, Ricardo Ney Oliveira Cobucci, Carlos André Nunes Jatobá, Thales Allyrio Araújo de Medeiros Fernandes, Judson Welber Verissimo de Azevedo, and Josélio Maria Galvão de Araújo. "The Role of the Mediators of Inflammation in Cancer Development." *Pathology & Oncology Research* 21, no. 3 (July 2015): 527–34.
- Ferrante, Daniela, Marinella Bertolotti, Annalisa Todesco, Dario Mirabelli, Benedetto Terracini, and Corrado Magnani. "Cancer Mortality and Incidence of Mesothelioma in a Cohort of Wives of Asbestos Workers in Casale Monferrato, Italy." *Environmental Health Perspectives* 115, no. 10 (October 2007): 1401–5.
- Ferrer, Jaume, Juan F. Montes, Maria A. Villarino, Richard W. Light, and José García-Valero. "Influence of Particle Size on Extrapleural Talc Dissemination after Talc Slurry Pleurodesis." *Chest* 122, no. 3 (September 2002): 1018–27.
- Fields, L., et al. "Gynecologic Cancer." Excerpt. *Clinical Oncology* 2001.
- Fiume, Monice M., Ivan Boyer, Wilma F. Bergfeld, Donald V. Belsito, Ronald A. Hill, Curtis D. Klaassen, Daniel C. Liebler, et al. "Safety Assessment of Talc as Used in Cosmetics." *International Journal of Toxicology* 34, no. 1 suppl (July 1, 2015): 66S-129S.
- Fletcher, Nicole M., Jimmy Belotte, Mohammed G. Saed, Ira Memaj, Michael P. Diamond, Robert T. Morris, and Ghassan M. Saed. "Specific Point Mutations in Key Redox Enzymes Are Associated with Chemoresistance in Epithelial Ovarian Cancer." *Free Radical Biology and Medicine* 102 (2017): 122–32.
- Fletcher, Nicole M., Zhongliang Jiang, Rouba Ali-Fehmi, Nancy K. Levin, Jimmy Belotte, Michael A. Tainsky, Michael P. Diamond, Husam M. Abu-Soud, and Ghassan M. Saed. "Myeloperoxidase and Free Iron Levels: Potential Biomarkers for Early Detection and Prognosis of Ovarian Cancer." *Cancer Biomarkers* 10 (2012 2011): 267–75.
- Fletcher, Nicole, Memaj, Ira, and Saed, Ghassan. "Talcum Powder Enhances Oxidative Stress in Ovarian Cancer Cells." *Reproductive Sciences*, February 28, 2018.
- Fletcher, NM, and GM Saed. "Talcum Powder Enhances Cancer Antigen 125 Levels in Ovarian Cancer Cells." *Presented at the 65th Meeting of the Society for Reproductive Investigation, San Diego, California*, 2018.
- Folkins, Ann K., Elke A. Jarboe, Jonathan L. Hecht, Michael G. Muto, and Christopher P. Crum. "Chapter 24 - Assessing Pelvic Epithelial Cancer Risk and Intercepting Early Malignancy." In *Diagnostic Gynecologic and Obstetric Pathology (Third Edition)*,

- 844–64. Philadelphia: Content Repository, 2018.
- Ford, D., D.F. Easton, M. Stratton, S. Narod, D. Goldgar, P. Devilee, D.T. Bishop, et al. “Genetic Heterogeneity and Penetrance Analysis of the BRCA1 and BRCA2 Genes in Breast Cancer Families.” *The American Journal of Human Genetics* 62, no. 3 (March 1998): 676–89.
- Frank, Czul and Lascano Jorge. “An Uncommon Hazard: Pulmonary Talcosis as a Result of Recurrent Aspiration of Baby Powder.” *Respiratory Medicine CME* No. 4 (2011): 109–111.
- Freedman, Ralph S, Michael Deavers, Jinsong Liu, and Ena Wang. “Peritoneal Inflammation – A Microenvironment for Epithelial Ovarian Cancer (EOC).” *Journal of Translational Medicine* 2, no. 23 (2004).
- Friebel, Tara M., Susan M. Domchek, and Timothy R. Rebbeck. “Modifiers of Cancer Risk in BRCA1 and BRCA2 Mutation Carriers: Systematic Review and Meta-Analysis.” *Journal of the National Cancer Institute* 106, no. 6 (June 2014): dju091.
- Frost, G. “The Latency Period of Mesothelioma among a Cohort of British Asbestos Workers (1978–2005).” *British Journal of Cancer* 109, no. 7 (October 1, 2013): 1965–73.
- Galea, Sandro, and Roger D. Vaughan. “Moving Beyond the Cause Constraint: A Public Health of Consequence, May 2018.” *American Journal of Public Health* 108, no. 5 (May 2018): 602–3.
- Gates, Margaret A., Bernard A. Rosner, Jonathan L. Hecht, and Shelley S. Tworoger. “Risk Factors for Epithelial Ovarian Cancer by Histologic Subtype.” *American Journal of Epidemiology* 171, no. 1 (January 1, 2010): 45–53.
- Gates, Margaret A., Shelley S. Tworoger, Kathryn L. Terry, Linda Titus-Ernstoff, Bernard Rosner, Immaculata De Vivo, Daniel W. Cramer, and Susan E. Hankinson. “Talc Use, Variants of the GSTM1, GSTT1, and NAT2 Genes, and Risk of Epithelial Ovarian Cancer.” *Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology* 17, no. 9 (September 2008): 2436–44.
- Genofre, Eduardo H., Francisco S. Vargas, Milena M. P. Acencio, Leila Antonangelo, Lisete R. Teixeira, and Evaldo Marchi. “Talc Pleurodesis: Evidence of Systemic Inflammatory Response to Small Size Talc Particles.” *Respiratory Medicine* 103, no. 1 (January 2009): 91–97.
- Germani, D., S. Belli, C. Bruno, M. Grignoli, M. Nesti, R. Pirastu, and P. Comba. “Cohort Mortality Study of Women Compensated for Asbestosis in Italy.” *American Journal of Industrial Medicine* 36, no. 1 (July 1999): 129–34.
- Gertig, D. M., D. J. Hunter, D. W. Cramer, G. A. Colditz, F. E. Speizer, W. C. Willett, and S. E. Hankinson. “Prospective Study of Talc Use and Ovarian Cancer.” *Journal of the National Cancer Institute* 92, no. 3 (February 2, 2000): 249–52.
- Ghio, Andrew J., Joleen M. Soukup, Lisa A. Dailey, Judy H. Richards, Jennifer L. Turi, Elizabeth N. Pavlisko, and Victor L. Roggli. “Disruption of Iron Homeostasis in Mesothelial Cells after Talc Pleurodesis.” *American Journal of Respiratory Cell and Molecular Biology* 46, no. 1 (January 1, 2012): 80–86.
- Gibbs, A.E., F.D. Pooley, M. Griffiths, R. Mitha, J.E. Craighead, J.R. Ruttner. “Talc Pneumoconiosis: A Pathologic and Mineralogic Study.” *Human Pathology* 23, No. 12, (December 1992): 1344–1354.
- Gloyne, S. R. “Two Cases of Squamous Carcinoma of the Lung Occurring in Asbestosis.”

- Tubercle* 17 (1935): 5–10.
- Godard, B., W. D. Foulkes, D. Provencher, J. S. Brunet, P. N. Tonin, A. M. Mes-Masson, S. A. Narod, and P. Ghadirian. “Risk Factors for Familial and Sporadic Ovarian Cancer among French Canadians: A Case-Control Study.” *American Journal of Obstetrics and Gynecology* 179, no. 2 (August 1998): 403–10.
- Gondal, M., et al. “Detection of Tox Metals (Lead and Chromium) in Talcum Powder Using Laser Induced Breakdown Spectroscopy.” *Applied Optics* 51, No. 30, (October 2012): 7395-7401.
- Gonzalez, Kelly D., Katie A. Noltner, Carolyn H. Buzin, Dongqing Gu, Cindy Y. Wen-Fong, Vu Q. Nguyen, Jennifer H. Han, et al. “Beyond Li Fraumeni Syndrome: Clinical Characteristics of Families with P53 Germline Mutations.” *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology* 27, no. 8 (March 10, 2009): 1250–56.
- Gonzalez, Nicole L., Katie M. O’Brien, Aimee A. D’Aloisio, Dale P. Sandler, and Clarice R. Weinberg. “Douching, Talc Use, and Risk of Ovarian Cancer.” *Epidemiology (Cambridge, Mass.)* 27, no. 6 (2016): 797–802.
- Goodman, Marc T, Galina Lurie, Pamela J Thompson, Katharine E McDuffie, and Michael E Carney. “Association of Two Common Single-Nucleotide Polymorphisms in the CYP19A1 Locus and Ovarian Cancer Risk.” *Endocrine-Related Cancer* 15, no. 4 (December 2008): 1055–60.
- Gordon, Ronald E., Sean Fitzgerald, and James Millette. “Asbestos in Commercial Cosmetic Talcum Powder as a Cause of Mesothelioma in Women.” *International Journal of Occupational and Environmental Health* 20, no. 4 (October 2014): 318–32.
- Graham, J., and R. Graham. “Ovarian Cancer and Asbestos.” *Environmental Research* 1, no. 2 (October 1967): 115–28.
- Graham, and Jenkins. “Value of Modified Starch as a Substitute for Talc.” *Lancet (London, England)* 1, no. 6708 (March 22, 1952): 590–91.
- Green, A., D. Purdie, C. Bain, V. Siskind, P. Russell, M. Quinn, and B. Ward. “Tubal Sterilisation, Hysterectomy and Decreased Risk of Ovarian Cancer. Survey of Women’s Health Study Group.” *International Journal of Cancer. Journal International Du Cancer* 71, no. 6 (June 11, 1997): 948–51.
- Grivennikov, Sergei I., Florian R. Greten, and Michael Karin. “Immunity, Inflammation, and Cancer.” *Cell* 140, no. 6 (March 19, 2010): 883–99.
- Gross, A. J., and P. H. Berg. “A Meta-Analytical Approach Examining the Potential Relationship between Talc Exposure and Ovarian Cancer.” *Journal of Exposure Analysis and Environmental Epidemiology* 5, no. 2 (June 1995): 181–95.
- Hall, J. M., M. K. Lee, B. Newman, J. E. Morrow, L. A. Anderson, B. Huey, and M. C. King. “Linkage of Early-Onset Familial Breast Cancer to Chromosome 17q21.” *Science (New York, N.Y.)* 250, no. 4988 (December 21, 1990): 1684–89.
- Halme, J., M. G. Hammond, J. F. Hulka, S. G. Raj, and L. M. Talbert. “Retrograde Menstruation in Healthy Women and in Patients with Endometriosis.” *Obstetrics and Gynecology* 64, no. 2 (August 1984): 151–54.
- Hamilton, T. C., H. Fox, C. H. Buckley, W. J. Henderson, and K. Griffiths. “Effects of Talc on the Rat Ovary.” *British Journal of Experimental Pathology* 65, no. 1 (February 1984): 101–6.
- Hanahan, Douglas and Robert A. Weinberg. “Hallmarks of Cancer: The Next Generation.” *Cell*

- 144, (March 4, 2011): 646-674.
- Hankinson, S. E., D. J. Hunter, G. A. Colditz, W. C. Willett, M. J. Stampfer, B. Rosner, C. H. Hennekens, and F. E. Speizer. "Tubal Ligation, Hysterectomy, and Risk of Ovarian Cancer. A Prospective Study." *JAMA* 270, no. 23 (December 15, 1993): 2813–18.
- Hannenhalli, Sridhar, and Klaus H. Kaestner. "The Evolution of Fox Genes and Their Role in Development and Disease." *Nature Reviews. Genetics* 10, no. 4 (April 2009): 233–40.
- Harlow, B. L., D. W. Cramer, D. A. Bell, and W. R. Welch. "Perineal Exposure to Talc and Ovarian Cancer Risk." *Obstetrics and Gynecology* 80, no. 1 (July 1992): 19–26.
- Harlow, B. L., and P. A. Hartge. "A Review of Perineal Talc Exposure and Risk of Ovarian Cancer." *Regulatory Toxicology and Pharmacology: RTP* 21, no. 2 (April 1995): 254–60.
- Harlow, B. L., and N. S. Weiss. "A Case-Control Study of Borderline Ovarian Tumors: The Influence of Perineal Exposure to Talc." *American Journal of Epidemiology* 130, no. 2 (August 1989): 390–94.
- Harper, Amy K, and Ghassan Saed. "'Talc Induces a pro-Oxidant State in Normal and Ovarian Cancer Cells through Genetic Point Mutations in Key Redox Enzymes,'" Accepted for Presentation at SGO Meeting," In Press 2019.
- Hartge, P., R. Hoover, L. P. Leshner, and L. McGowan. "Talc and Ovarian Cancer." *JAMA: The Journal of the American Medical Association* 250, no. 14 (October 14, 1983): 1844.
- Hasselbalch, Hans Carl. "Chronic Inflammation as a Promotor of Mutagenesis in Essential Thrombocythemia, Polycythemia Vera and Myelofibrosis. A Human Inflammation Model for Cancer Development?" *Leukemia Research* 37, no. 2 (February 2013): 214–20.
- Havrilesky, Laura J., Patricia G. Moorman, William J. Lowery, Jennifer M. Gierisch, Remy R. Coeytaux, Rachel Peragallo Urrutia, Michaela Dinan, et al. "Oral Contraceptive Pills as Primary Prevention for Ovarian Cancer: A Systematic Review and Meta-Analysis." *Obstetrics and Gynecology* 122, no. 1 (July 2013): 139–47.
- Heller, D. S., R. E. Gordon, and N. Katz. "Correlation of Asbestos Fiber Burdens in Fallopian Tubes and Ovarian Tissue." *American Journal of Obstetrics and Gynecology* 181, no. 2 (August 1999): 346–47.
- Heller, D. S., R. E. Gordon, C. Westhoff, and S. Gerber. "Asbestos Exposure and Ovarian Fiber Burden." *American Journal of Industrial Medicine* 29, no. 5 (May 1996): 435–39.
- Heller, D. S., C. Westhoff, R. E. Gordon, and N. Katz. "The Relationship between Perineal Cosmetic Talc Usage and Ovarian Talc Particle Burden." *American Journal of Obstetrics and Gynecology* 174, no. 5 (May 1996): 1507–10.
- Henderson, W. J., T. C. Hamilton, M. S. Baylis, C. G. Pierrepont, and K. Griffiths. "The Demonstration of the Migration of Talc from the Vagina and Posterior Uterus to the Ovary in the Rat." *Environmental Research* 40, no. 2 (August 1986): 247–50.
- Henderson, W. J., T. C. Hamilton, and K. Griffiths. "Talc in Normal and Malignant Ovarian Tissue." *The Lancet* (March 3, 1979): 499.
- Henderson, W. J., C. A. Joslin, A. C. Turnbull, and K. Griffiths. "Talc and Carcinoma of the Ovary and Cervix." *The Journal of Obstetrics and Gynaecology of the British Commonwealth* 78, no. 3 (March 1971): 266–72.
- Hernán, Miguel A. "The C-Word: Scientific Euphemisms Do Not Improve Causal Inference From Observational Data." *American Journal of Public Health* 108, no. 5 (May 2018): 616–19.
- Hill, Austin Bradford. "The Environment and Disease: Association or Causation?" *Proceedings*

- of the Royal Society of Medicine* 58, no. 5 (May 1965): 295–300.
- Hillegass, Jedd M., Arti Shukla, Maximilian B. MacPherson, Jeffrey P. Bond, Chad Steele, and Brooke T. Mossman. “Utilization of Gene Profiling and Proteomics to Determine Mineral Pathogenicity in a Human Mesothelial Cell Line (LP9/TERT-1).” *Journal of Toxicology and Environmental Health. Part A* 73, no. 5 (January 2010): 423–36.
- Hollinger, Manfred. “Pulmonary Toxicity of Inhaled and Intravenous Talc.” *Toxicology Letters* 52 (1990): 121–127.
- Horowitz, Neil S., Austin Miller, Bunja Rungruang, Scott D. Richard, Noah Rodriguez, Michael A. Bookman, Chad A. Hamilton, Thomas C. Krivak, and G. Larry Maxwell. “Does Aggressive Surgery Improve Outcomes? Interaction between Preoperative Disease Burden and Complex Surgery in Patients with Advanced-Stage Ovarian Cancer: An Analysis of GOG 182.” *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology* 33, no. 8 (March 10, 2015): 937–43.
- Houghton, Serena C., Katherine W. Reeves, Susan E. Hankinson, Lori Crawford, Dorothy Lane, Jean Wactawski-Wende, Cynthia A. Thomson, Judith K. Ockene, and Susan R. Sturgeon. “Perineal Powder Use and Risk of Ovarian Cancer.” *Journal of the National Cancer Institute* 106, no. 9 (September 2014).
- Huncharek, Michael, J. F. Geschwind, and Bruce Kupelnick. “Perineal Application of Cosmetic Talc and Risk of Invasive Epithelial Ovarian Cancer: A Meta-Analysis of 11,933 Subjects from Sixteen Observational Studies.” *Anticancer Research* 23, no. 2C (April 2003): 1955–60.
- Huncharek, Michael, Joshua Muscat, Adedayo Onitilo, and Bruce Kupelnick. “Use of Cosmetic Talc on Contraceptive Diaphragms and Risk of Ovarian Cancer: A Meta-Analysis of Nine Observational Studies.” *European Journal of Cancer Prevention: The Official Journal of the European Cancer Prevention Organisation (ECP)* 16, no. 5 (October 2007): 422–29.
- Hunn, Jessica, and Gustavo C. Rodriguez. “Ovarian Cancer: Etiology, Risk Factors, and Epidemiology.” *Clinical Obstetrics and Gynecology* 55, no. 1 (March 2012): 3–23.
- IARC. “Mechanisms of Fibre Carcinogens.” *IARC Scientific Publications*. No. 140. 1996.
- IARC. “IARC Monographs on the Evaluation of Carcinogenic Risks to Humans – IARC: Asbestos,” 1977.
- IARC. “IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 58. Beryllium, Cadmium, Mercury, and Exposures in the Glass Manufacturing Industry,” 1993.
- IARC. “IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 93 Carbon Black, Titanium Dioxide, and Talc.” *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans / World Health Organization, International Agency for Research on Cancer* 93 (2010): 1–413.
- IARC. “IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Volume 100C,” 2012.
- IARC. “IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Silica and Some Silicates.” IARC, 1987.
- IARC. “IARC Monographs on the Evaluation of the Carcinogenic Risks to Humans. Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1–42. Supplement 7,” 1987.
- IARC, International Agency for Research on Cancer, and World Health Organization, eds.

- Carbon Black, Titanium Dioxide, and Talc*. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, v. 93. Lyon, France: Geneva: International Agency for Research on Cancer; Distributed by WHO Press, 2010.
- “Inflammation: A Hidden Path to Breaking the Spell of Ovarian Cancer.” *Cell Cycle* 8, no. 19 (2009): 3107–11.
- Institute of Medicine (US) Committee on Asbestos: Selected Health Effects. *Asbestos: Selected Cancers*. The National Academies Collection: Reports Funded by National Institutes of Health. Washington (DC): National Academies Press (US), 2006.
- Isaacs, Claudine, and Beth N Peshkin. “Management of Patients at High Risk for Breast and Ovarian Cancer.” *UpToDate*, 2018.
- Iturralde, M., and P. F. Venter. “Hysterosalpingo-Radionuclide Scintigraphy (HERS).” *Seminars in Nuclear Medicine* 11, no. 4 (October 1981): 301–14.
- J. Lightfoot, G.A. Kingston, and F.D. Pooley. “An Examination of Italian Mine Samples and Relevant Powders,” 1972.
- Jaiswal, M., N. F. LaRusso, L. J. Burgart, and G. J. Gores. “Inflammatory Cytokines Induce DNA Damage and Inhibit DNA Repair in Cholangiocarcinoma Cells by a Nitric Oxide-Dependent Mechanism.” *Cancer Research* 60, no. 1 (January 1, 2000): 184–90.
- “JANSSEN-000056 P-23 (Pltf_MISC_00000321) Ortho Diaphragm Information,” n.d.
- Jasuja, S. et al. “Cosmetic Talc-Related Pulmonary Granulomatosis.” *Journal of Investigative Medicine High Impact Case Reports* (July-September 2017): 1–4.
- Jaurand, M. C. “Mechanisms of Fiber-Induced Genotoxicity.” *Environmental Health Perspectives* 105 Suppl 5 (September 1997): 1073–84.
- Jaurand, M. C. “Particulate-State Carcinogenesis: A Survey of Recent Studies on the Mechanisms of Action of Fibres.” *IARC Scientific Publications*, no. 90 (1989): 54–73.
- Jaurand, MC. “Mechanisms of Fibre Genotoxicity.” In *Mechanisms in Fibre Carcinogenesis*. New York: Plenum Press, 1991.
- Jervis, Sarah, Honglin Song, Andrew Lee, Ed Dicks, Jonathan Tyrer, Patricia Harrington, Douglas F. Easton, Ian J. Jacobs, Paul P. D. Pharoah, and Antonis C. Antoniou. “Ovarian Cancer Familial Relative Risks by Tumour Subtypes and by Known Ovarian Cancer Genetic Susceptibility Variants.” *Journal of Medical Genetics* 51, no. 2 (February 2014): 108–13.
- Jia, D, Y Nagaoka, S Orsulic, and M Katsumata. “Inflammation Is a Key Contributor to Ovarian Cancer Cell Seeding.” *Scientific Reports* 8, no. 12394 (August 17, 2018).
- Jiang, Zhongliang, Nicole M. Fletcher, Rouba Ali-Fehmi, Michael P. Diamond, Husam M. Abu-Soud, Adnan R. Munkarah, and Ghassan M. Saed. “Modulation of Redox Signaling Promotes Apoptosis in Epithelial Ovarian Cancer Cells.” *Gynecologic Oncology* 122, no. 2 (August 2011): 418–23.
- John M. DeSesso. “Exponent Talc Defense Presentation Toxic Talc?” January 18, 2018.
- Jones, Richard E., and Kristin H. Lopez. “Human Reproductive Biology - 4th Edition Chapter 9 - Gamete Transport and Fertilization.” In *Human Reproductive Biology*, Third., 159–73. San Diego: Academic Press, 2006.
- Jordan, SJ, KL Cushing-Haugen, KG Wicklund, JA Doherty, and MA Rossing. “Breast Feeding and Risk of Epithelial Ovarian Cancer.” *Cancer Causes & Control: CCC* 23, no. 6 (June 2012): 919–27.
- Jordan, Susan J., Victor Siskind, Adèle C Green, David C. Whiteman, and Penelope M. Webb. “Breastfeeding and Risk of Epithelial Ovarian Cancer.” *Cancer Causes & Control: CCC*

- 21, no. 1 (January 2010): 109–16.
- Jordan, Susan J., David C. Whiteman, David M. Purdie, Adèle C. Green, and Penelope M. Webb. “Does Smoking Increase Risk of Ovarian Cancer? A Systematic Review.” *Gynecologic Oncology* 103, no. 3 (December 2006): 1122–29.
- Jurinski, Joseph B., and J. Donald Rimstidt. “Biodurability of Talc.” *American Mineralogist* 86, no. 4 (April 2001): 392–99.
- Kane, AB, P Boffetta, R Saracci, and JD Wilbourn. “Mechanisms of Fibre Carcinogenesis.” IARC, 1996.
- Kang, N., D. Griffin, and H. Ellis. “The Pathological Effects of Glove and Condom Dusting Powders.” *Journal of Applied Toxicology* 12, no. 6 (December 1992): 443–49.
- Kanterman, J., Moshe Sade-Feldman, Michal Baniyash. “New Insights into Chronic Inflammation-Induced Immunosuppression.” *Seminars in Cancer Biology* 22 (2012): 307– 318.
- Karageorgi, Stalo, Margaret A. Gates, Susan E. Hankinson, and Immaculata De Vivo. “Perineal Use of Talcum Powder and Endometrial Cancer Risk.” *Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology* 19, no. 5 (May 2010): 1269–75.
- Kasper, C. S., and P. J. Chandler. “Possible Morbidity in Women from Talc on Condoms.” *JAMA: The Journal of the American Medical Association* 273, no. 11 (March 15, 1995): 846–47.
- Kauff, Noah D., Nandita Mitra, Mark E. Robson, Karen E. Hurley, Shaokun Chuai, Deborah Goldfrank, Eve Wadsworth, et al. “Risk of Ovarian Cancer in BRCA1 and BRCA2 Mutation-Negative Hereditary Breast Cancer Families.” *Journal of the National Cancer Institute* 97, no. 18 (September 21, 2005): 1382–84.
- Keal, E.E. “Asbestosis and Abdominal Neoplasms.” *The Lancet* (December 3, 1960): 1211-1260.
- Keskin, Nadi, Yasemin Aktan Teksen, Esra Gürlek Ongun, Yusuf Ozay, and Halil Saygili. “Does Long-Term Talc Exposure Have a Carcinogenic Effect on the Female Genital System of Rats? An Experimental Pilot Study.” *Archives of Gynecology and Obstetrics* 280, no. 6 (December 2009): 925–31.
- Khan, Mohd Imran, AmoghA. Sahasrabuddhe, Govil Patil, Mohd Javed Akhtar, Mohd Ashquin, and Iqbal Ahmad. “Nano-Talc Stabilizes TNF- α m-RNA in Human Macrophages.” *Journal of Biomedical Nanotechnology* 7, no. 1 (January 1, 2011): 112–13.
- King, HM. “Talc: The Softest Mineral.”
- King, Talmadge. “Asbestos-Related Pleuropulmonary Disease.” Edited by Kevin Flaherty. *UpToDate*, 2018.
- Kiraly, Orsolya, Guanyu Gong, Werner Olipitz, Sureshkumar Muthupalani, and Bevin P. Engelward. “Inflammation-Induced Cell Proliferation Potentiates DNA Damage-Induced Mutations In Vivo.” *PLoS Genetics*, February 3, 2015.
- Kissler, Stefan, Ernst Siebzehnuebl, Joachim Kohl, Anja Mueller, Nadja Hamscho, Regine Gaetje, Andre Ahr, Achim Rody, and Manfred Kaufmann. “Uterine Contractility and Directed Sperm Transport Assessed by Hysterosalpingoscintigraphy (HSSG) and Intrauterine Pressure (IUP) Measurement.” *Acta Obstetrica Et Gynecologica Scandinavica* 83, no. 4 (April 2004): 369–74.
- Klampfer, Lidija. “Cytokines, Inflammation and Colon Cancer.” *Current Cancer Drug Targets*

- 11, no. 4 (May 2011): 451–64.
- Knudson, A. G. “Mutation and Cancer: Statistical Study of Retinoblastoma.” *Proceedings of the National Academy of Sciences of the United States of America* 68, no. 4 (April 1971): 820–23.
- Kunz, G., D. Beil, H. Deiniger, A. Einspanier, G. Mall, and G. Leyendecker. “The Uterine Peristaltic Pump. Normal and Impeded Sperm Transport within the Female Genital Tract.” *Advances in Experimental Medicine and Biology* 424 (1997): 267–77.
- Kurman, Robert J., and Ie-Ming Shih. “Molecular Pathogenesis and Extraovarian Origin of Epithelial Ovarian Cancer. Shifting the Paradigm.” *Human Pathology* 42, no. 7 (July 2011): 918–31.
- Kurman, Robert J. “The Dualistic Model of Ovarian Carcinogenesis.” *The American Journal of Pathology* 186, no. 4 (April 1, 2016): 733–47.
- Kurman, Robert J., “The Origin and Pathogenesis of Epithelial Ovarian Cancer: A Proposed Unifying Theory.” *The American Journal of Surgical Pathology* 34, no. 3 (March 2010): 433–43.
- Kurta, Michelle L., Kirsten B. Moysich, Joel L. Weissfeld, Ada O. Youk, Clareann H. Bunker, Robert P. Edwards, Francesmary Modugno, Roberta B. Ness, and Brenda Diergaarde. “Use of Fertility Drugs and Risk of Ovarian Cancer: Results from a US-Based Case-Control Study.” *Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology* 21, no. 8 (August 2012): 1282–92.
- La Vecchia. “Ovarian Cancer: Epidemiology and Risk Factors.” *European Journal of Cancer Prevention* 26 (2017): 55–62.
- Lambert, C., et al. “A Case-Control Study of Mesothelioma in Minnesota Iron Ore (Taconite) Miners.” *Occup Environ Med* 73 (2016):103–109.
- Lancaster, Johnathan M., C. Bethan Powell, Lee-may Chen, and Debra L. Richardson. “Society of Gynecologic Oncology Statement on Risk Assessment for Inherited Gynecologic Cancer Predispositions.” *Gynecologic Oncology* 136, no. 1 (January 2015): 3–7.
- Landen, Charles N., Michael J. Birrer, and Anil K. Sood. “Early Events in the Pathogenesis of Epithelial Ovarian Cancer.” *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology* 26, no. 6 (February 20, 2008): 995–1005.
- Langseth, H., S. E. Hankinson, J. Siemiatycki, and E. Weiderpass. “Perineal Use of Talc and Risk of Ovarian Cancer.” *Journal of Epidemiology and Community Health* 62, no. 4 (April 2008): 358–60.
- Langseth, H., B.V. Johansen, J.M. Nesland, and K. Kjaerheim. “Asbestos Fibers in Ovarian Tissue from Norwegian Pulp and Paper Workers.” *International Journal of Gynecological Cancer* 17, no. 1 (January 2007): 44–49.
- Langseth, Hilde, and Kristina Kjaerheim. “Ovarian Cancer and Occupational Exposure among Pulp and Paper Employees in Norway.” *Scandinavian Journal of Work, Environment & Health* 30, no. 5 (October 2004): 356–61.
- Lanphear, B. P., and C. R. Buncher. “Latent Period for Malignant Mesothelioma of Occupational Origin.” *Journal of Occupational Medicine.: Official Publication of the Industrial Medical Association* 34, no. 7 (July 1992): 718–21.
- Lee, Jennifer S., Esther M. John, Valerie McGuire, Anna Felberg, Kimberly L. Ostrow, Richard A. DiCioccio, Frederick P. Li, Alexander Miron, Dee W. West, and Alice S. Whittemore. “Breast and Ovarian Cancer in Relatives of Cancer Patients, with and without BRCA

- Mutations.” *Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology* 15, no. 2 (February 2006): 359–63.
- Leikauf, George. “Toxic Responses of the Respiratory System.” Chapter 15. 2013.
- Levanon, Keren, Christopher Crum, and Ronny Drapkin. “New Insights into the Pathogenesis of Serous Ovarian Cancer and Its Clinical Impact.” *Journal of Clinical Oncology* 26, no. 32 (November 10, 2008): 5284–93.
- Levy-Lahad, E., and E. Friedman. “Cancer Risks among BRCA1 and BRCA2 Mutation Carriers.” *British Journal of Cancer* 96, no. 1 (January 15, 2007): 11–15.
- Levy, Stuart. “Pulmonary Reactions to Other Occupational Dusts and Fumes.” *Occupational Medicine*. 3rd Edition. Mosby. 1994.
- Lin, Hui-Wen, Ying-Yueh Tu, Shiyng Yu Lin, Wei-Ju Su, Wei Li Lin, Wei Zer Lin, Shen-Chi Wu, and Yuen-Liang Lai. “Risk of Ovarian Cancer in Women with Pelvic Inflammatory Disease: A Population-Based Study.” *The Lancet. Oncology* 12, no. 9 (September 2011): 900–904.
- Liou, Geou-Yarh, and Peter Storz. “Reactive Oxygen Species in Cancer.” *Free Radical Research* 44, no. 5 (May 2010): 476–96.
- Liu, D. T., and A. Hitchcock. “Endometriosis: Its Association with Retrograde Menstruation, Dysmenorrhoea and Tubal Pathology.” *British Journal of Obstetrics and Gynaecology* 93, no. 8 (August 1986): 859–62.
- Lo-Ciganic, Wei-Hsuan, Janice C. Zgibor, Clareann H. Bunker, Kirsten B. Moysich, Robert P. Edwards, and Roberta B. Ness. “Aspirin, Nonaspirin Nonsteroidal Anti-Inflammatory Drugs, or Acetaminophen and Risk of Ovarian Cancer.” *Epidemiology (Cambridge, Mass.)* 23, no. 2 (March 2012): 311–19.
- Lockey, J. E. “Nonasbestos Fibrous Minerals.” *Clinics in Chest Medicine* 2, no. 2 (May 1981): 203–18.
- Longo, D. L., and R. C. Young. “Cosmetic Talc and Ovarian Cancer.” *Lancet* 2, no. 8138 (August 18, 1979): 349–51.
- Luan, Nan-Nan, Qi-Jun Wu, Ting-Ting Gong, Emily Vogtmann, Yong-Lai Wang, and Bei Lin. “Breastfeeding and Ovarian Cancer Risk: A Meta-Analysis of Epidemiologic Studies1234.” *The American Journal of Clinical Nutrition* 98, no. 4 (October 2013): 1020–31.
- Lundin, Eva, Laure Dossus, Tess Clendenen, Vittorio Krogh, Kjell Grankvist, Marianne Wulff, Sabina Sieri, et al. “C-Reactive Protein and Ovarian Cancer: A Prospective Study Nested in Three Cohorts (Sweden, USA, Italy).” *Cancer Causes & Control: CCC* 20, no. 7 (September 2009): 1151–59.
- Madsen, Cecilie, Louise Baandrup, Christian Dehlendorff, and Susanne K. Kjaer. “Tubal Ligation and Salpingectomy and the Risk of Epithelial Ovarian Cancer and Borderline Ovarian Tumors: A Nationwide Case-Control Study.” *Acta Obstetrica Et Gynecologica Scandinavica* 94, no. 1 (January 2015): 86–94.
- Magnani, C., D. Ferrante, F. Barone-Adesi, M. Bertolotti, A. Todesco, D. Mirabelli, and B. Terracini. “Cancer Risk after Cessation of Asbestos Exposure: A Cohort Study of Italian Asbestos Cement Workers.” *Occupational and Environmental Medicine* 65, no. 3 (March 2008): 164–70.
- Mäki-Nevala, Satu, Virinder Kaur Sarhadi, Aija Knuuttila, Ilari Scheinin, Pekka Ellonen, Sonja Lagström, Mikko Rönty, et al. “Driver Gene and Novel Mutations in Asbestos-Exposed

- Lung Adenocarcinoma and Malignant Mesothelioma Detected by Exome Sequencing.” *Lung* 194, no. 1 (February 2016): 125–35.
- Mallen, Adrienne R., Mary K. Townsend, and Shelley S. Tworoger. “Risk Factors for Ovarian Carcinoma.” *Hematology/Oncology Clinics of North America*, September 2018.
- Mandel, J., et al. “A Review of Mortality Associated with Elongate Mineral Particle (EMP) Exposure in Occupational Epidemiology Studies of Gold, Talc, and Taconite Mining.” *American Journal of Industrial Medicine* 59 (2016): 1047-1060.
- Mannino, David M. “Cigarette Smoking and Other Possible Risk Factors for Lung Cancer.” *UpToDate*, 2018.
- Mattenklott, M. “Asbestos in Talc Powders and Soapstone – The Present State.” *Gefahrstoffe-Reinhalt.* Luft 67 No. 7/8 (2007): 287-291.
- McCullough, Marie. “Condom Makers Stop Using Talc.” *Asbury Park Press*. January 16, 1996.
- McCullough, Marie. “Women’s Health Concerns Prompt Condom Makers to Stop Using Talc.” *Jersey Journal*. April 17, 1996, City Edition.
- McLaughlin-Drubin, Margaret E., and Karl Munger. “Viruses Associated with Human Cancer.” *Biochimica et Biophysica Acta* 1782, no. 3 (March 2008): 127–50.
- McLemore, Miaskowski, Chen Aouizerat, and Dodd. “Epidemiological and Genetic Factors Associated With Ovarian Cancer.” *Cancer Nursing* 32, no. 4 (2009): 281–88.
- Melaiu, Ombretta, Federica Gemignani, and Stefano Landi. “The Genetic Susceptibility in the Development of Malignant Pleural Mesothelioma.” *Journal of Thoracic Disease* 10, no. Suppl 2 (January 2018): S246–52.
- Meng, Qingsong, Weixue Sun, John Jiang, Nicole M. Fletcher, Michael P. Diamond, and Ghassan M. Saed. “Identification of Common Mechanisms between Endometriosis and Ovarian Cancer.” *Journal of Assisted Reproduction and Genetics* 28 (2011): 917–23.
- Merritt, Melissa A., Adèle C. Green, Christina M. Nagle, Penelope M. Webb, Australian Cancer Study (Ovarian Cancer), and Australian Ovarian Cancer Study Group. “Talcum Powder, Chronic Pelvic Inflammation and NSAIDs in Relation to Risk of Epithelial Ovarian Cancer.” *International Journal of Cancer. Journal International Du Cancer* 122, no. 1 (January 1, 2008): 170–76.
- Miller, Diane M, and Jessica N. McAlpine. “Opportunistic Salpingectomy for Ovarian, Fallopian Tubal, and Peritoneal Carcinoma Risk Reduction.” *UpToDate*, 2018.
- Mills, Paul K., Deborah G. Riordan, Rosemary D. Cress, and Heather A. Young. “Perineal Talc Exposure and Epithelial Ovarian Cancer Risk in the Central Valley of California.” *International Journal of Cancer. Journal International Du Cancer* 112, no. 3 (November 10, 2004): 458–64.
- Milne, R. L., and A. C. Antoniou. “Genetic Modifiers of Cancer Risk for BRCA1 and BRCA2 Mutation Carriers.” *Annals of Oncology: Official Journal of the European Society for Medical Oncology* 22 Suppl 1 (January 2011): i11-17.
- Milne, Roger L., and Antonis C. Antoniou. “Modifiers of Breast and Ovarian Cancer Risks for BRCA1 and BRCA2 Mutation Carriers.” *Endocrine-Related Cancer* 23, no. 10 (2016): T69-84.
- Moller, Danielsen, and Roursgaard Jantzen. “Oxidatively Damaged DNA in Animals Exposed to Particles.” *Critical Reviews in Toxicology* 43, no. 2 (2013): 96–118.
- Moon, Min Chaul, Jung Duck Park, Byung Soon Choi, So Young Park, Dong Won Kim, Yong Hyun Chung, Naomi Hisanaga, and Il Je Yu. “Risk Assessment of Baby Powder Exposure through Inhalation.” *Toxicological Research* 27, no. 3 (September 2011):

- 137–41.
- Moorman, Patricia G. “Scientific Review of the Epidemiologic Evidence on Talc Use and Ovarian Cancer,” February 2018.
- Moorman, Patricia G., Rachel T. Palmieri, Lucy Akushevich, Andrew Berchuck, and Joellen M. Schildkraut. “Ovarian Cancer Risk Factors in African-American and White Women.” *American Journal of Epidemiology* 170, no. 5 (September 1, 2009): 598–606.
- Moskowitz, Robert. “Talc Pneumoconiosis: A Treated Case.” *Chest* 58, No.1 (July 1970): 37-41.
- Mostafa, S. A., C. B. Barger, R. W. Flower, N. B. Rosenshein, T. H. Parmley, and J. D. Woodruff. “Foreign Body Granulomas in Normal Ovaries.” *Obstetrics and Gynecology* 66, no. 5 (November 1985): 701–2.
- Murphy, Megan A., Britton Trabert, Hannah P. Yang, Yikyung Park, Louise A. Brinton, Patricia Hartge, Mark E. Sherman, Albert Hollenbeck, and Nicolas Wentzensen. “Non-Steroidal Anti-Inflammatory Drug Use and Ovarian Cancer Risk: Findings from the NIH-AARP Diet and Health Study and Systematic Review.” *Cancer Causes & Control: CCC* 23, no. 11 (November 2012): 1839–52.
- Muscat, J. E., and M. S. Huncharek. “Causation and Disease: Biomedical Science in Toxic Tort Litigation.” *Journal of Occupational Medicine: Official Publication of the Industrial Medical Association* 31, no. 12 (December 1989): 997–1002.
- Nadler, Diana L., and Igor G. Zurbenko. “Estimating Cancer Latency Times Using a Weibull Model,” 2014, 8.
- Nam, Key and Douglas R. Gracey. “Pulmonary Talcosis from Cosmetic Talcum Powder.” *JAMA* 221, No. 5 (1972): 492-493.
- Narod, Steven A. “Talc and Ovarian Cancer.” *Gynecologic Oncology* 141, no. 3 (2016): 410–12.
- National Cancer Institute, Surveillance, Epidemiology, and End Results Program. “Cancer Stat Facts: Ovarian Cancer,” 2018.
- National Cancer Institute. “NCI Dictionary of Cancer Terms: Pleurodesis.”
- “National Toxicology Program (NTP) Technical Report (NTP TR 421) on the Toxicology and Carcinogenesis Studies of Talc in F344/N Rats and B6C3F1 Mice.” National Institutes of Health, 1993.
- Nelson, Heather H., and Karl T. Kelsey. “The Molecular Epidemiology of Asbestos and Tobacco in Lung Cancer.” *Oncogene* 21, no. 48 (October 21, 2002): 7284–88.
- Ness, R. B., and C. Cottreau. “Possible Role of Ovarian Epithelial Inflammation in Ovarian Cancer.” *JNCI Journal of the National Cancer Institute* 91, no. 17 (September 1, 1999): 1459–67.
- Ness, R. B., J. A. Grisso, C. Cottreau, J. Klapper, R. Vergona, J. E. Wheeler, M. Morgan, and J. J. Schlesselman. “Factors Related to Inflammation of the Ovarian Epithelium and Risk of Ovarian Cancer.” *Epidemiology (Cambridge, Mass.)* 11, no. 2 (March 2000): 111–17.
- Ness, Roberta B., Daniel W. Cramer, Marc T. Goodman, Susanne Krüger Kjaer, Kathy Mallin, Berit Jul Mosgaard, David M. Purdie, Harvey A. Risch, Ronald Vergona, and Anna H. Wu. “Infertility, Fertility Drugs, and Ovarian Cancer: A Pooled Analysis of Case-Control Studies.” *American Journal of Epidemiology* 155, no. 3 (February 1, 2002): 217–24.
- Neutra, Raymond Richard, Carl F. Cranor, and David Gee. “The Use and Misuse of Bradford Hill in U.S. Tort Law.” *Jurimetrics J.*, 2018, 127–62.
- Newhouse, M. L., G. Berry, J. C. Wagner, and M. E. Turok. “A Study of the Mortality of Female Asbestos Workers.” *British Journal of Industrial Medicine* 29, no. 2 (April 1972): 134–41.

- Nick, Alpa M., Robert L. Coleman, Pedro T. Ramirez, and Anil K. Sood. "A Framework for a Personalized Surgical Approach to Ovarian Cancer." *Nature Reviews. Clinical Oncology* 12, no. 4 (April 2015): 239–45.
- NIOSH. "Asbestos Fibers and Other Elongated Mineral Particles: State of the Science and Roadmap for Research (Revised Draft)," January 2009.
- NIOSH. "Fiber Exposure during Use of Baby Powders, Report No. IWS-36-6.," July 1972.
- NIOSH. 2011 Current Intelligence Bulletin No. 62," 2011.
- NIOSH. "Pocket Guide to Chemical Hazards: Asbestos." Publication No. 2005-149 (September 2007).
- Norquist, Barbara M., Maria I. Harrell, Mark F. Brady, Tom Walsh, Ming K. Lee, Suleyman Gulsuner, Sarah S. Bernards, et al. "Inherited Mutations in Women With Ovarian Carcinoma." *JAMA Oncology* 2, no. 4 (April 2016): 482–90.
- NTP. "Report on Carcinogens: Asbestos." 14th Edition. 2016.
- NTP. "NTP Technical Report on the Toxicology and Carcinogenesis Studies of Benzophenone (CAS No. 119-61-9) In F344/N Rats and B6C3F1 Mice," February 2006.
- NTP. "NTP Toxicology and Carcinogenesis Studies of Talc (CAS No. 14807-96-6)(NonAsbestiform) in F344/N.Rats and B6C3F1 Mice (Inhalation Studies)," 1993.
- Oberdörster, Günter, Eva Oberdörster, and Jan Oberdörster. "Nanotoxicology: An Emerging Discipline Evolving from Studies of Ultrafine Particles." *Environmental Health Perspectives* 113, no. 7 (July 2005): 823–39. <https://doi.org/10.1289/ehp.7339>.
- Okada, Futoshi. "Beyond Foreign-Body-Induced Carcinogenesis: Impact of Reactive Oxygen Species Derived from Inflammatory Cells in Tumorigenic Conversion and Tumor Progression." *International Journal of Cancer* 121, no. 11 (December 1, 2007): 2364–72.
- Paoletti, L., S. Caiazza, G. Donelli, and F. Pocchiari. "Evaluation by Electron Microscopy Techniques of Asbestos Contamination in Industrial, Cosmetic, and Pharmaceutical Talcs." *Regulatory Toxicology and Pharmacology: RTP* 4, no. 3 (September 1984): 222–35.
- Park, Hyo K., Joellen M. Schildkraut, Anthony J. Alberg, Elisa V. Bandera, Jill S. Barnholtz-Sloan, Melissa Bondy, Sydnee Crankshaw, et al. "Benign Gynecologic Conditions Are Associated with Ovarian Cancer Risk in African-American Women: A Case–Control Study." *Cancer Causes & Control*, September 29, 2018.
- Parmar, M. K. B., J. A. Ledermann, N. Colombo, A. du Bois, J.-F. Delaloye, G. B. Kristensen, S. Wheeler, et al. "Paclitaxel plus Platinum-Based Chemotherapy versus Conventional Platinum-Based Chemotherapy in Women with Relapsed Ovarian Cancer: The ICON4/AGO-OVAR-2.2 Trial." *Lancet (London, England)* 361, no. 9375 (June 21, 2003): 2099–2106.
- Parmley, T. H., and J. D. Woodruff. "The Ovarian Mesothelioma." *American Journal of Obstetrics and Gynecology* 120, no. 2 (September 15, 1974): 234–41.
- Pathology of Asbestos-Associated Diseases*, 2011.
- Pearce, Celeste Leigh, Claire Templeman, Mary Anne Rossing, Alice Lee, Aimee M Near, Penelope M Webb, Christina M Nagle, et al. "Association between Endometriosis and Risk of Histological Subtypes of Ovarian Cancer: A Pooled Analysis of Case–Control Studies." *The Lancet Oncology* 13, no. 4 (April 2012): 385–94. [https://doi.org/10.1016/S1470-2045\(11\)70404-1](https://doi.org/10.1016/S1470-2045(11)70404-1).
- Pejovic, Tanja, and Farr Nezhat. "Missing Link: Inflammation and Ovarian Cancer." *The Lancet*.

- Oncology* 12, no. 9 (September 2011): 833–34.
- Pelling, D., and J. G. Evans. “Long-Term Peritoneal Tissue Response in Rats to Mould-Release Agents and Lubricant Powder Used on Surgeons’ Gloves.” *Food and Chemical Toxicology: An International Journal Published for the British Industrial Biological Research Association* 24, no. 5 (May 1986): 425–30.
- Penninkilampi, Ross, and Guy D. Eslick. “Perineal Talc Use and Ovarian Cancer: A Systematic Review and Meta-Analysis.” *Epidemiology (Cambridge, Mass.)* 29, no. 1 (January 2018): 41–49.
- Peshkin, B., et al. “Genetic Counseling and Testing for Hereditary Breast and Ovarian Cancer - UpToDate,” 2018.
https://www.uptodate.com/contents/genetic-counseling-and-testing-for-hereditary-breast-and-ovarian-cancer?search=Genetic%20counseling%20and%20testing%20for%20hereditary%20breast%20and%20ovarian%20cancer&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1.
- Peshkin, B. “Overview of Hereditary Breast and Ovarian Cancer Syndromes - UpToDate,” 2018.
https://www.uptodate.com/contents/overview-of-hereditary-breast-and-ovarian-cancer-syndromes?search=Overview%20of%20hereditary%20breast%20and%20ovarian%20cancer%20syndromes&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1.
- Peshkin, B. “Prevalence of BRCA1 and BRCA2 Mutations and Associated Cancer Risks - UpToDate,” 2018.
https://www.uptodate.com/contents/prevalence-of-brca1-and-brca2-mutations-and-associated-cancer-risks?search=prevalence-of-brca1-and-brca2-mu%E2%80%A6search_result%26selectedTitle%3D1~73%26usage_type%3Ddefault%26display_rank%3D1&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2.
- Phillips, J. C., P. J. Young, K. Hardy, and S. D. Gangolli. “Studies on the Absorption and Disposition of 3H-Labelled Talc in the Rat, Mouse, Guinea-Pig and Rabbit.” *Food and Cosmetics Toxicology* 16, no. 2 (April 1978): 161–63.
- Pira, E, C Pelucchi, L Buffoni, A Palmas, M Turbiglio, E Negri, P G Piolatto, and C La Vecchia. “Cancer Mortality in a Cohort of Asbestos Textile Workers.” *British Journal of Cancer* 92, no. 3 (February 2005): 580–86.
- Pira, Enrico, Canzio Romano, Francesco S. Violante, Andrea Farioli, Giovanna Spatari, Carlo La Vecchia, and Paolo Boffetta. “Updated Mortality Study of a Cohort of Asbestos Textile Workers.” *Cancer Medicine* 5, no. 9 (2016): 2623–28.
- Porro, F. W., and N. M. Levine. “Pathology of Talc Pneumoconiosis with Report of an Autopsy.” *Northern New York Medical Journal* 3 (April 1946): 23–25.
- Pott, R., and K. H. Friedrichs. “Tumors in Rats Following i.p. Injection of Fiberform Dusts.” *Naturwissenschaften* 59 (n.d.): 318–24.
- Prat, Jaime, and FIGO Committee on Gynecologic Oncology. “Abridged Republication of FIGO’s Staging Classification for Cancer of the Ovary, Fallopian Tube, and Peritoneum.” *Cancer* 121, no. 19 (October 1, 2015): 3452–54.
- Pukkala, Eero, Jan Ivar Martinsen, Elsebeth Lynge, Holmfridur Kolbrun Gunnarsdottir, Pär Sparén, Laufey Tryggvadottir, Elisabete Weiderpass, and Kristina Kjaerheim. “Occupation and Cancer - Follow-up of 15 Million People in Five Nordic Countries.” *Acta Oncologica (Stockholm, Sweden)* 48, no. 5 (2009): 646–790.
- Purdie, D., A. Green, C. Bain, V. Siskind, B. Ward, N. Hacker, M. Quinn, G. Wright, P. Russell,

- and B. Susil. "Reproductive and Other Factors and Risk of Epithelial Ovarian Cancer: An Australian Case-Control Study. Survey of Women's Health Study Group." *International Journal of Cancer. Journal International Du Cancer* 62, no. 6 (September 15, 1995): 678–84.
- Purdie, David M., Christopher J. Bain, Victor Siskind, Penelope M. Webb, and Adèle C. Green. "Ovulation and Risk of Epithelial Ovarian Cancer." *International Journal of Cancer. Journal International Du Cancer* 104, no. 2 (March 20, 2003): 228–32.
- Radic, I, I Vucak, J Milosevic, A Marusic, S Vukicevic, and M Marusic. "Immunosuppression Induced by Talc Granulomatosis in the Rat." *Clinical and Experimental Immunology* 73, no. 2 (August 1988): 316–21.
- Ramus, Susan J., Antonis C. Antoniou, Karoline B. Kuchenbaecker, Penny Soucy, Jonathan Beesley, Xiaqing Chen, Lesley McGuffog, et al. "Ovarian Cancer Susceptibility Alleles and Risk of Ovarian Cancer in BRCA1 and BRCA2 Mutation Carriers." *Human Mutation* 33, no. 4 (April 2012): 690–702.
- Rasool, Nabila, Amanda Nickles Fader, Leigh Seamon, Nikki L. Neubauer, Fadi Abu Shahin, Heather A. Alexander, Kathleen Moore, et al. "Stage I, Grade 3 Endometrioid Adenocarcinoma of the Endometrium: An Analysis of Clinical Outcomes and Patterns of Recurrence." *Gynecologic Oncology* 116, no. 1 (January 2010): 10–14.
- Rayburn, Elizabeth R., Scharri J. Ezell, and Ruiwen Zhang. "Anti-Inflammatory Agents for Cancer Therapy." *Molecular and Cellular Pharmacology* 1, no. 1 (2009): 29–43.
- Rebbeck, Timothy R., Nandita Mitra, Fei Wan, Olga M. Sinilnikova, Sue Healey, Lesley McGuffog, Sylvie Mazoyer, et al. "Association of Type and Location of BRCA1 and BRCA2 Mutations with Risk of Breast and Ovarian Cancer." *JAMA* 313, no. 13 (April 7, 2015): 1347–61.
- "Reference Manual on Scientific Evidence" Third Edition (2011).
- Rehman, Ghana, et al. "Determination of Toxic Heavy Metals in Different Brands of Talcum Powder." *International Journal of Applied and Natural Sciences (IJANS)*; Vol. 2, Issue 2; (May 2013): 45-52.
- Reid, A., J. Heyworth, N. de Klerk, and A. W. Musk. "The Mortality of Women Exposed Environmentally and Domestically to Blue Asbestos at Wittenoom, Western Australia." *Occupational and Environmental Medicine* 65, no. 11 (November 2008): 743–49.
- Reid, A., N. de Klerk, and A. W. Musk. "Does Exposure to Asbestos Cause Ovarian Cancer? A Systematic Literature Review and Meta-Analysis." *Cancer Epidemiology Biomarkers & Prevention* 20, no. 7 (July 1, 2011): 1287–95.
- Reid, A., N. H. de Klerk, C. Magnani, D. Ferrante, G. Berry, A. W. Musk, and E. Merler. "Mesothelioma Risk after 40 Years since First Exposure to Asbestos: A Pooled Analysis." *Thorax* 69, no. 9 (September 2014): 843–50.
- Reid, Alison, Amanda Segal, Jane S. Heyworth, Nicholas H. de Klerk, and Arthur W. Musk. "Gynecologic and Breast Cancers in Women after Exposure to Blue Asbestos at Wittenoom." *Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology* 18, no. 1 (January 2009): 140–47.
- Reid, Brett M., Jennifer B. Permuth, and Thomas A. Sellers. "Epidemiology of Ovarian Cancer: A Review." *Cancer Biology & Medicine* 14, no. 1 (February 2017): 9–32.
- Reinhold, Robert. "Panel Finds Danger to the Environment from Technology." *New York Times*; (December 29, 1968).

- Reuter, Simone, Subash C. Gupta, Madan M. Chaturvedi, and Bharat B. Aggarwal. "Oxidative Stress, Inflammation, and Cancer: How Are They Linked?" *Free Radical Biology and Medicine* 49, no. 11 (December 1, 2010): 1603–16.
- Rice, Megan S., Susan E. Hankinson, and Shelley S. Tworoger. "Tubal Ligation, Hysterectomy, Unilateral Oophorectomy, and Risk of Ovarian Cancer in the Nurses' Health Studies." *Fertility and Sterility* 102, no. 1 (July 2014): 192-198.e3. <https://doi.org/10.1016/j.fertnstert.2014.03.041>.
- Ring, Kari L., Christine Garcia, Martha H. Thomas, and Susan C. Modesitt. "Current and Future Role of Genetic Screening in Gynecologic Malignancies." *American Journal of Obstetrics and Gynecology* 217, no. 5 (2017): 512–21.
- Riska, A., J. I. Martinsen, K. Kjaerheim, E. Lynge, P. Sparen, L. Tryggvadottir, E. Weiderpass, and E. Pukkala. "Occupation and Risk of Primary Fallopian Tube Carcinoma in Nordic Countries." *International Journal of Cancer* 131, no. 1 (July 1, 2012): 186–92. <https://doi.org/10.1002/ijc.26337>.
- Roggli, Victor L., Robin T. Vollmer, Kelly J. Butnor, and Thomas A. Sporn. "Tremolite and Mesothelioma." *Annals of Occupational Hygiene* 46, no. 5 (July 1, 2002): 447–53.
- Rohl, A. N. "Asbestos in Talc." *Environmental Health Perspectives* 9 (December 1974): 129–32.
- Rohl, A. N., A. M. Langer, I. J. Selikoff, A. Tordini, R. Klimentidis, D. R. Bowes, and D. L. Skinner. "Consumer Talcums and Powders: Mineral and Chemical Characterization." *Journal of Toxicology and Environmental Health* 2, no. 2 (November 1976): 255–84.
- Roodhouse Gloyne, S. "Two Cases of Squamous Carcinoma of the Lung Occurring in Asbestosis." *Tubercle* 17, no. 1 (October 1935): 5-IN2.
- Rosalind A. Eeles, Christine D. Berg, and Jeffery S. Tobias. *Cancer Prevention and Screening: Concepts, Principles and Controversies*. 1st ed. Accessed August 21, 2018. Rosenblatt, K. A., M. Szklo, and N. B. Rosenshein. "Mineral Fiber Exposure and the Development of Ovarian Cancer." *Gynecologic Oncology* 45, no. 1 (April 1992): 20–25.
- Rosenblatt, Karin A., Noel S. Weiss, Kara L. Cushing-Haugen, Kristine G. Wicklund, and Mary Anne Rossing. "Genital Powder Exposure and the Risk of Epithelial Ovarian Cancer." *Cancer Causes & Control: CCC* 22, no. 5 (May 2011): 737–42.
- Rösler, J. A., H. J. Woitowitz, H. J. Lange, R. H. Woitowitz, K. Ulm, and K. Rödelberger. "Mortality Rates in a Female Cohort Following Asbestos Exposure in Germany." *Journal of Occupational Medicine.: Official Publication of the Industrial Medical Association* 36, no. 8 (August 1994): 889–93.
- Ross, M. "Geology, Asbestos, and Health." *Environmental Health Perspectives* 9 (December 1974): 123–24.
- Rothman, Kenneth J., Sander Greenland, and Timothy L. Lash. *Modern Epidemiology*. Lippincott Williams & Wilkins, 2008.
- Saed, Ghassan M., Rouba Ali-Fehmi, Zhong L. Jiang, Nicole M. Fletcher, Michael P. Diamond, Husam M. Abu-Soud, and Adnan R. Munkarah. "Myeloperoxidase Serves as a Redox Switch That Regulates Apoptosis in Epithelial Ovarian Cancer." *Gynecologic Oncology* 116, no. 2 (February 2010): 276–81. <https://doi.org/10.1016/j.ygyno.2009.11.004>.
- Saed, Ghassan M., Michael P. Diamond, and Nicole M. Fletcher. "Updates of the Role of Oxidative Stress in the Pathogenesis of Ovarian Cancer." *Gynecologic Oncology* 145, no. 3 (June 2017): 595–602. <https://doi.org/10.1016/j.ygyno.2017.02.033>.
- Saed, Ghassan M., Nicole M. Fletcher, Michael P. Diamond, Robert T. Morris, Nardhy Gomez-Lopez, and Ira Memaj. "Novel Expression of CD11b in Epithelial Ovarian

- Cancer: Potential Therapeutic Target.” *Gynecologic Oncology* 148, no. 3 (2018): 567–75.
- Saed, Ghassan M., Robert T. Morris, and Nicole M. Fletcher. *New Insights into the Pathogenesis of Ovarian Cancer: Oxidative Stress*, 2018.
- Schelz, John P. “The Detection of Chrysotile Asbestos at Low Levels in Talc by Differential Thermal Analysis.” *Thermochimica Acta*, 8 (1974) 197-204.
- Schenken, Robert S. “Endometriosis: Pathogenesis, Clinical Features, and Diagnosis.” *UpToDate*, 2018.
- Schildkraut, Joellen M., Sarah E. Abbott, Anthony J. Alberg, Elisa V. Bandera, Jill S. Barnholtz-Sloan, Melissa L. Bondy, Michele L. Cote, et al. “Association between Body Powder Use and Ovarian Cancer: The African American Cancer Epidemiology Study (AACES).” *Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology* 25, no. 10 (2016): 1411–17.
- Seeler, Albert O., M.D. “Toxic Hazards, Talc Pneumoconiosis.” *The New England Journal of Medicine*; Vol. 261, No. 21 (Nov. 19, 1959) 1084-1085.
- “SEER Cancer Statistics Review, 1975-2015, National Cancer Institute, Bethesda, MD, Based on November 2017 SEER Data Submission, Posted to the SEER Web Site,” April 2018.
- Selikoff, Irving J., et al. “Asbestos Exposure and Neoplasia.” *JAMA*, Vol. 188, No. 1 (April 6, 1964) 142-146.
- Shan, Weiwei, and Jinsong Liu. “Inflammation: A Hidden Path to Breaking the Spell of Ovarian Cancer.” *Cell Cycle* 8, no. 19 (2009): 3107–11.
- Shukla, Arti, Maximilian B. MacPherson, Jedd Hillegass, Maria E. Ramos-Nino, Vlada Alexeeva, Pamela M. Vacek, Jeffrey P. Bond, Harvey I. Pass, Chad Steele, and Brooke T. Mossman. “Alterations in Gene Expression in Human Mesothelial Cells Correlate with Mineral Pathogenicity.” *American Journal of Respiratory Cell and Molecular Biology* 41, no. 1 (July 2009): 114–23.
- Shushan, A., O. Paltiel, J. Iscovich, U. Elchalal, T. Peretz, and J. G. Schenker. “Human Menopausal Gonadotropin and the Risk of Epithelial Ovarian Cancer.” *Fertility and Sterility* 65, no. 1 (January 1996): 13–18.
- Singh, Naveena, C. Blake Gilks, Lynn Hirschowitz, Sean Kehoe, Iain A. McNeish, Dianne Miller, Raj Naik, Nafisa Wilkinson, and W. Glenn McCluggage. “Primary Site Assignment in Tubo-Ovarian High-Grade Serous Carcinoma: Consensus Statement on Unifying Practice Worldwide.” *Gynecologic Oncology* 141, no. 2 (2016): 195–98.
- Sjösten, A. C. E., H. Ellis, and G. a. B. Edlstrom. “Retrograde Migration of Glove Powder in the Human Female Genital Tract.” *Human Reproduction* 19, no. 4 (April 1, 2004): 991–95.
- Soini, Tuuli, Ritva Hurskainen, Seija Grénman, Johanna Mäenpää, Jorma Paavonen, and Eero Pukkala. “Cancer Risk in Women Using the Levonorgestrel-Releasing Intrauterine System in Finland.” *Obstetrics and Gynecology* 124, no. 2 Pt 1 (August 2014): 292–99.
- Soong, Thing Rinda, Brooke E. Howitt, Alexander Miron, Neil S. Horowitz, Frank Campbell, Colleen M. Feltmate, Michael G. Muto, et al. “Evidence for Lineage Continuity between Early Serous Proliferations (ESPs) in the Fallopian Tube and Disseminated High-Grade Serous Carcinomas.” *The Journal of Pathology*, July 25, 2018.
- Stanton, M. F., M. Layard, A. Tegeris, E. Miller, M. May, E. Morgan, and A. Smith. “Relation of Particle Dimension to Carcinogenicity in Amphibole Asbestos and Other Fibrous Minerals.” *Journal of the National Cancer Institute* 67, no. 5 (November 1981): 965–75.
- Starman, Daniel H., Leslie A. Litzky, and Larry R. Kaiser. “Epidemiology of Malignant Pleural

- Mesothelioma.” *UpToDate*, 2018.
- Steiling, W., J. F. Almeida, H. Assaf Vandecasteele, S. Gilpin, T. Kawamoto, L. O’Keeffe, G. Pappa, K. Rettinger, H. Rothe, and A. M. Bowden. “Principles for the Safety Evaluation of Cosmetic Powders.” *Toxicology Letters*, August 17, 2018.
- Steiling, W., M. Bascompta, P. Carthew, G. Catalano, N. Corea, A. D’Haese, P. Jackson, et al. “Principle Considerations for the Risk Assessment of Sprayed Consumer Products.” *Toxicology Letters* 227, no. 1 (May 16, 2014): 41–49.
- Stewart, Louise M., C. D’Arcy J. Holman, Patrick Aboagye-Sarfo, Judith C. Finn, David B. Preen, and Roger Hart. “In Vitro Fertilization, Endometriosis, Nulliparity and Ovarian Cancer Risk.” *Gynecologic Oncology* 128, no. 2 (February 2013): 260–64.
- Stewart, Louise M., Katrina Spilsbury, Susan Jordan, Colin Stewart, C. D’Arcy J. Holman, Aime Powell, Joanne Reekie, and Paul Cohen. “Risk of High-Grade Serous Ovarian Cancer Associated with Pelvic Inflammatory Disease, Parity and Breast Cancer.” *Cancer Epidemiology* 55 (August 2018): 110–16.
- Straif, Kurt. “Update of the Scientific Evidence on Asbestos and Cancer.” presented at the International Conference on Environmental and Occupational Determinants of Cancer: Interventions for Primary Prevention, Asturias (Avilés, Gijón), Spain, March 17, 2011.
- Suzui, Masumi, et al. “Multiwalled Carbon Nanotubes Intratracheally Instilled into the Rat Lung Induce Development of Pleural Malignant Mesothelioma and Lung Tumors.” *Cancer Sci*, 107 (2016) 924-935.
- “Talc.” *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans* 42 (1987): 185–224.
- Tarchi, M., D. Orsi, P. Comba, M. De Santis, R. Pirastu, G. Battista, and M. Valiani. “Cohort Mortality Study of Rock Salt Workers in Italy.” *American Journal of Industrial Medicine* 25, no. 2 (February 1994): 251–56.
- Terry, Kathryn L., Stalo Karageorgi, Yurii B. Shvetsov, Melissa A. Merritt, Galina Lurie, Pamela J. Thompson, Michael E. Carney, et al. “Genital Powder Use and Risk of Ovarian Cancer: A Pooled Analysis of 8,525 Cases and 9,859 Controls.” *Cancer Prevention Research (Philadelphia, Pa.)* 6, no. 8 (August 2013): 811–21.
- Tewari, Devansu, James J. Java, Ritu Salani, Deborah K. Armstrong, Maurie Markman, Thomas Herzog, Bradley J. Monk, and John K. Chan. “Long-Term Survival Advantage and Prognostic Factors Associated with Intraperitoneal Chemotherapy Treatment in Advanced Ovarian Cancer: A Gynecologic Oncology Group Study.” *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology* 33, no. 13 (May 1, 2015): 1460–66.
- Thai, T. H., F. Du, J. T. Tsan, Y. Jin, A. Phung, M. A. Spillman, H. F. Massa, et al. “Mutations in the BRCA1-Associated RING Domain (BARD1) Gene in Primary Breast, Ovarian and Uterine Cancers.” *Human Molecular Genetics* 7, no. 2 (February 1998): 195–202.
- Thomas, Charles A., and Major G. Seelig. Powder lubricated surgeon’s rubber glove. United States US2621333A, filed June 27, 1947, and issued December 16, 1952.
- Torre, Lindsey A., Britton Trabert, Carol E. DeSantis, Kimberly D. Miller, Goli Samimi, Carolyn D. Runowicz, Mia M. Gaudet, Ahmedin Jemal, and Rebecca L. Siegel. “Ovarian Cancer Statistics, 2018.” *CA: A Cancer Journal for Clinicians* 68, no. 4 (July 2018): 284–96.
- Trabert, Britton. “Body Powder and Ovarian Cancer Risk – What Is the Role of Recall Bias?” *Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American*

- Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology* 25, no. 10 (October 2016): 1369–70.
- Trabert, Britton, Ligia Pinto, Patricia Hartge, Troy Kemp, Amanda Black, Mark E. Sherman, Louise A. Brinton, et al. “Pre-Diagnostic Serum Levels of Inflammation Markers and Risk of Ovarian Cancer in the Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) Screening Trial.” *Gynecologic Oncology* 135, no. 2 (November 2014): 297–304.
- Trabert, Britton, Elizabeth M Poole, Emily White, Kala Visvanathan, Hans-Olov Adami, Garnet L Anderson, Theodore M Brasky, et al. “Analgesic Use and Ovarian Cancer Risk: An Analysis in the Ovarian Cancer Cohort Consortium.” *JNCI: Journal of the National Cancer Institute* 111, no. 2 (2019).
- Trabert, Britton, Elizabeth M. Poole, Emily White, Kala Visvanathan, Hans-Olov Adami, Garnet L. Anderson, Theodore M. Brasky, et al. “Analgesic Use and Ovarian Cancer Risk: An Analysis in the Ovarian Cancer Cohort Consortium.” *Journal of the National Cancer Institute* 111, no. 2 (2019).
- Tsilidis, K K, N E Allen, T J Key, L Dossus, A Lukanova, K Bakken, E Lund, et al. “Oral Contraceptive Use and Reproductive Factors and Risk of Ovarian Cancer in the European Prospective Investigation into Cancer and Nutrition.” *British Journal of Cancer* 105, no. 9 (October 25, 2011): 1436–42.
- Tsilidis, Konstantinos K., Naomi E. Allen, Timothy J. Key, Laure Dossus, Rudolf Kaaks, Kjersti Bakken, Eiliv Lund, et al. “Menopausal Hormone Therapy and Risk of Ovarian Cancer in the European Prospective Investigation into Cancer and Nutrition.” *Cancer Causes & Control: CCC* 22, no. 8 (August 2011): 1075–84.
- Twohig, Shelley S., Kathleen M. Fairfield, Graham A. Colditz, Bernard A. Rosner, and Susan E. Hankinson. “Association of Oral Contraceptive Use, Other Contraceptive Methods, and Infertility with Ovarian Cancer Risk.” *American Journal of Epidemiology* 166, no. 8 (October 15, 2007): 894–901.
- Tzonou, A., A. Polychronopoulou, C. C. Hsieh, A. Rebelakos, A. Karakatsani, and D. Trichopoulos. “Hair Dyes, Analgesics, Tranquilizers and Perineal Talc Application as Risk Factors for Ovarian Cancer.” *International Journal of Cancer. Journal International Du Cancer* 55, no. 3 (September 30, 1993): 408–10.
- US EPA. “Health Assessment Document for Talc. | National Technical Reports Library - NTIS.” -600/8-91/217, 1992.
- Vallyathan, N. Val, Ph.D., et al. “Pulmonary Pathology in Workers Exposed to Nonasbestiform Talc.” *Human Pathology*, Vol. 12, No. 1 (January 1981) 28-35.
- Van Gosen, B. S., H.A. Lowers, S.J. Sutley, and C.A. Gent. “Using the Geologic Setting of Talc Deposits as an Indicator of Amphibole Asbestos Content.” *Environmental Geology* 45, no. 7 (2004): 20.
- Van Huisstede, A., et al. “Talcosis Due to Abundant Use of Cosmetic Talcum Powder.” *European Respiratory Review*, Vol. 19, No. 116 (2010) 165-168.
- Vanderhyden, Barbara C, Tanya J Shaw, and Jean-François Ethier. “Animal Models of Ovarian Cancer.” *Reproductive Biology and Endocrinology: RB&E* 1 (October 7, 2003): 67.
- VanOrden, D. “Weight Percent Compositional Analysis of Seven RTV Talc Samples. Analytical Report to R. T. Vanderbilt Company, Inc. Submitted to Public Comments Record – C. W. Jameson, National Toxicology Program, 10th ROC Nominations ‘Talc (Containing Asbestiform Fibers)’ 4 December 2000., National Toxicology Program.” November 22, 2000.
- Vasama-Neuvonen, K., E. Pukkala, H. Paakkulainen, P. Mutanen, E. Weiderpass, P. Boffetta, N.

- Shen, T. Kauppinen, H. Vainio, and T. Partanen. "Ovarian Cancer and Occupational Exposures in Finland." *American Journal of Industrial Medicine* 36, no. 1 (July 1999): 83–89.
- Vasey, Paul A., Gordon C. Jayson, Alan Gordon, Hani Gabra, Rob Coleman, Ronnie Atkinson, David Parkin, et al. "Phase III Randomized Trial of Docetaxel-Carboplatin versus Paclitaxel-Carboplatin as First-Line Chemotherapy for Ovarian Carcinoma." *Journal of the National Cancer Institute* 96, no. 22 (November 17, 2004): 1682–91.
- Venkatesan, Priya. "Possible X Chromosome-Linked Transmission of Ovarian Cancer." *The Lancet. Oncology* 19, no. 4 (April 2018): e185.
- Venter, P. F., and M. Iturralde. "Migration of a Particulate Radioactive Tracer from the Vagina to the Peritoneal Cavity and Ovaries." *South African Medical Journal = Suid-Afrikaanse Tydskrif Vir Geneeskunde* 55, no. 23 (June 2, 1979): 917–19.
- Verdoodt, Freija, Christian Dehlendorff, Søren Friis, and Susanne K. Kjaer. "Non-Aspirin NSAID Use and Ovarian Cancer Mortality." *Gynecologic Oncology* 150, no. 2 (2018): 331–37. <https://doi.org/10.1016/j.ygyno.2018.06.018>.
- Vicus, Danielle, Amy Finch, Barry Rosen, Isabel Fan, Linda Bradley, Ilana Cass, Ping Sun, et al. "Risk Factors for Carcinoma of the Fallopian Tube in Women with and without a Germline BRCA Mutation." *Gynecologic Oncology* 118, no. 2 (August 1, 2010): 155–59. <https://doi.org/10.1016/j.ygyno.2010.03.009>.
- Vineis, Paolo, Phyllis Illari, and Federica Russo. "Causality in Cancer Research: A Journey through Models in Molecular Epidemiology and Their Philosophical Interpretation." *Emerging Themes in Epidemiology* 14, no. 7 (2017).
- Virta, RL. "The Phase Relationship of Talc and Amphiboles in a Fibrous Talc Sample." IH; Report of Investigations, 1985. <https://www.cdc.gov/niosh/nioshtic-2/10004328.html>.
- Vitonis, Allison F., Linda Titus-Ernstoff, and Daniel W. Cramer. "Assessing Ovarian Cancer Risk When Considering Elective Oophorectomy at the Time of Hysterectomy." *Obstetrics and Gynecology* 117, no. 5 (May 2011): 1042–50.
- Wang, Chunpeng, Zhenzhen Liang, Xin Liu, Qian Zhang, and Shuang Li. "The Association between Endometriosis, Tubal Ligation, Hysterectomy and Epithelial Ovarian Cancer: Meta-Analyses." *International Journal of Environmental Research and Public Health* 13, no. 11 (November 14, 2016): 1138.
- Wang, Dingzhi, et al. "Immunosuppression Associated with Chronic Inflammation in the Tumor Microenvironment." *Carcinogenesis*, Vol. 36, No. 10 (2015): 1085-1093.
- Wang, Xiaorong, Sihao Lin, Ignatius Yu, Hong Qiu, Yajia Lan, and Eiji Yano. "Cause-Specific Mortality in a Chinese Chrysotile Textile Worker Cohort." *Cancer Science* 104, no. 2 (February 2013): 245–49.
- Watson, Ian R., Koichi Takahashi, P. Andrew Futreal, and Lynda Chin. "Emerging Patterns of Somatic Mutations in Cancer." *Nature Reviews. Genetics* 14, no. 10 (October 2013): 703–18.
- Wehner, A. P., A. S. Hall, R. E. Weller, E. A. Lepel, and R. E. Schirmer. "Do Particles Translocate from the Vagina to the Oviducts and Beyond?" *Food and Chemical Toxicology: An International Journal Published for the British Industrial Biological Research Association* 23, no. 3 (March 1985): 367–72.
- Wehner, A. P., R. E. Weller, and E. A. Lepel. "On Talc Translocation from the Vagina to the Oviducts and Beyond." *Food and Chemical Toxicology: An International Journal Published for the British Industrial Biological Research Association* 24, no. 4 (April

- 1986): 329–38.
- Weiss, W. “Cigarette Smoking and Lung Cancer Trends. A Light at the End of the Tunnel?” *Chest* 111, no. 5 (May 1997): 1414–16.
- Wells, I.P., et al. “Pulmonary Disease Caused By the Inhalation of Cosmetic Talcum Powder.” *British Journal of Radiology*, Vol. 52, No. 619; (July 1979) 586-588.
- Wentzensen, Nicolas, Elizabeth M. Poole, Britton Trabert, Emily White, Alan A. Arslan, Alpa V. Patel, V. Wendy Setiawan, et al. “Ovarian Cancer Risk Factors by Histologic Subtype: An Analysis from the Ovarian Cancer Cohort Consortium.” *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology* 34, no. 24 (2016): 2888–98.
- Werner, I. “Presence of Asbestos in Talc Samples.” *Atenschutzinform* 21, no. 5 (1982).
- West, Sophie D., et al. “Pleurodesis for Malignant Pleural Effusions: Current Controversies and Variations in Practices.” *Curr Opin Pulm Med* 10, *Diseases in the Pleura*, (2004) 305-310.
- Whiteman, David C., Michael F. G. Murphy, Linda S. Cook, Daniel W. Cramer, Patricia Hartge, Polly A. Marchbanks, Philip C. Nasca, Roberta B. Ness, David M. Purdie, and Harvey A. Risch. “Multiple Births and Risk of Epithelial Ovarian Cancer.” *Journal of the National Cancer Institute* 92, no. 14 (July 19, 2000): 1172–77.
- Whittemore, A. S., R. Harris, and J. Itnyre. “Characteristics Relating to Ovarian Cancer Risk: Collaborative Analysis of 12 US Case-Control Studies. IV. The Pathogenesis of Epithelial Ovarian Cancer. Collaborative Ovarian Cancer Group.” *American Journal of Epidemiology* 136, no. 10 (November 15, 1992): 1212–20.
- Whittemore, A. S., M. L. Wu, R. S. Paffenbarger, D. L. Sarles, J. B. Kampert, S. Grosser, D. L. Jung, S. Ballon, and M. Hendrickson. “Personal and Environmental Characteristics Related to Epithelial Ovarian Cancer. II. Exposures to Talcum Powder, Tobacco, Alcohol, and Coffee.” *American Journal of Epidemiology* 128, no. 6 (December 1988): 1228–40.
- Whysner, J., and M. Mohan. “Perineal Application of Talc and Cornstarch Powders: Evaluation of Ovarian Cancer Risk.” *American Journal of Obstetrics and Gynecology* 182, no. 3 (March 2000): 720–24.
- Wignall, B.K., and A.J. Fox. “Mortality of Female Gas Mask Assemblers.” *British Journal of Industrial Medicine* 39, no. 1 (1982): 34–38.
- Wild, P. “Lung Cancer Risk and Talc Not Containing Asbestiform Fibres: A Review of the Epidemiological Evidence.” *Occupational and Environmental Medicine* 63, no. 1 (January 2006): 4–9.
- Wolff, Henrik, Tapio Vehmas, Panu Oksa, Jorma Rantanen, and Harri Vainio. “Asbestos, Asbestosis, and Cancer, the Helsinki Criteria for Diagnosis and Attribution 2014: Recommendations.” *Scandinavian Journal of Work, Environment & Health* 41, no. 1 (January 2015): 5–15.
- Wong, C., R. E. Hempling, M. S. Piver, N. Natarajan, and C. J. Mettlin. “Perineal Talc Exposure and Subsequent Epithelial Ovarian Cancer: A Case-Control Study.” *Obstetrics and Gynecology* 93, no. 3 (March 1999): 372–76.
- Woodruff, J. D. “The Pathogenesis of Ovarian Neoplasia.” *The Johns Hopkins Medical Journal* 144, no. 4 (April 1979): 117–20.
- Wright, H. R., J. C. Wheeler, J. A. Woods, J. Hesford, P. Taylor, and R. F. Edlich. “Potential Toxicity of Retrograde Uterine Passage of Particulate Matter.” *Journal of Long-Term*

- Effects of Medical Implants* 6, no. 3–4 (1996): 199–206.
- Wu, A. H., C. L. Pearce, C.-C. Tseng, and M. C. Pike. “African Americans and Hispanics Remain at Lower Risk of Ovarian Cancer Than Non-Hispanic Whites after Considering Nongenetic Risk Factors and Oophorectomy Rates.” *Cancer Epidemiology Biomarkers & Prevention* 24, no. 7 (July 1, 2015): 1094–1100.
- Wu, Anna H., Celeste L. Pearce, Chiu-Chen Tseng, and Malcolm C. Pike. “African Americans and Hispanics Remain at Lower Risk of Ovarian Cancer Than Non-Hispanic Whites after Considering Nongenetic Risk Factors and Oophorectomy Rates.” *Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology* 24, no. 7 (July 2015): 1094–1100.
- Wu, Anna H., Celeste L. Pearce, Chiu-Chen Tseng, Claire Templeman, and Malcolm C. Pike. “Markers of Inflammation and Risk of Ovarian Cancer in Los Angeles County.” *International Journal of Cancer. Journal International Du Cancer* 124, no. 6 (March 15, 2009): 1409–15.
- Wu, Song, Wei Zhu, Patricia Thompson, and Yusuf A. Hannun. “Evaluating Intrinsic and Non-Intrinsic Cancer Risk Factors.” *Nature Communications* 9, no. 1 (August 28, 2018): 3490.
- Yan, Bin, Yuanlin Peng, and Chuan-Yuan Li. “Molecular Analysis of Genetic Instability Caused by Chronic Inflammation.” *Methods in Molecular Biology (Clifton, N.J.)* 512 (2009): 15–28.
- Yan, Bin, Huili Wang, Zahid Rabbani, Yulin Zhao, Wenrong Li, Yuqing Yuan, Fang Li, Mark W. Dewhirst, and Chuan-Yuan Li. “Tumor Necrosis Factor- α Is a Potent Endogenous Mutagen That Promotes Cellular Transformation.” *Cancer Research* 66 (December 15, 2006): 11565.
- “You Can Steer Clients to Condoms Free from Potentially Harmful Talc: Condom Companies Agree to Produce without the Dry Lubricant.” *Contraceptive Technology Update* 16, no. 11 (November 1995): 133–44.
- Zazenski, R., W. H. Ashton, D. Briggs, M. Chudkowski, J. W. Kelse, L. MacEachern, E. F. McCarthy, M. A. Nordhauser, M. T. Roddy, and N. M. Teetsel. “Talc: Occurrence, Characterization, and Consumer Applications.” *Regulatory Toxicology and Pharmacology: RTP* 21, no. 2 (April 1995): 218–29.
- Zervomanoklakis, I, H.W. Ott, D Hadziomerovic, V. Mattle, B.E. Seeber, I. Virgolini, D. Heute, S. Kissler, G. Leyendecker, and L. Wildt. “Physiology of Upward Transport in the Human Female Genital Tract.” *Annals of New York Academy of Sciences* 1101, no. 1 (2007): 1–20.
- Zhao, Weixing, Justin B. Steinfeld, Fengshan Liang, Xiaoyong Chen, David G. Maranon, Chu Jian Ma, Youngho Kwon, et al. “BRCA1-BARD1 Promotes RAD51-Mediated Homologous DNA Pairing.” *Nature* 550, no. 7676 (19 2017): 360–65.

DEPOSITIONS, TRANSCRIPTS AND REPORTS:

Affidavit of Laura Plunkett, PhD 02.22.18

Deposition of Alice Blount in the Ingham v. J&J Matter on 04.13.18

Deposition of Annie Awanaiss Yessian on 07.13.2017

Deposition and Exhibits of Pat Downey Dated 8.7.18-8.8.18
Deposition and Exhibits of John Hopkins Dated 8.16.18-8.17.18, 10.17.18 and 11.05.18
Deposition and Exhibits of Susan Nicholson Dated 7.26.18-7.27.18
Deposition and Exhibits of Julie Pier Dated 9.12.18-9.13.18
Ingham v. J&J Volume 11 (Egilman, Koman, Martinez, Packard) 6-14-18
Ingham v. J&J Volume 14A (Madigan, Williams) 6-20-18
Ingham v. JJ Volume 24A (Warner Huh, MD) 7.5.18
Ingham v. JJ Volume 24B (Warner Huh, MD) 7.5.18
John J. Godleski Expert Report for Brower Matter Dated 6.23.18
Lanzo Plaintiffs MIL re Imerys Spoliation and Concealment of Talc Samples
Laura Plunkett - Supplemental Expert Brower Report
Longo Analysis of J&J's Historical Talc Samples from the 1960's
Longo Analysis of J&J's Historical Talc Samples from the 1970's
Longo Analysis of J&J's Historical Talc Samples from the 1980's
Longo Analysis of J&J's Historical Talc Samples from the 1990's
Longo Analysis of J&J's Baby Powder Historical Samples - Asian - October 2018
Longo Analysis of J&J's BP Talc Products for Amphibole (Tremolite) Asbestos 8.2.17
Longo Analysis Report_Exhibit BB_04.28.2017
Longo MAS Project 14-1852 Below the Waist Application of Johnson's BP 9.2017
Longo Process Blanks for the Analysis of J&J's Products from the 60's to 90's for Asbestos
Longo TEM Analysis of Historical 1978 Johnson's BP Sample for Amphibole Asbestos 2.16.18
Longo Verification of Lee Poye's TEM Analysis of J&J's Historical Vermont Talc 11.5.18
Michael Crowley Expert Report Dated 11.12.18
Report of Results: MVA11730 Investigation of Italian Talc Samples for Asbestos 08.01.2017
RJLEE-001497
Thomas Dydek Brower Expert Report Dated 8.16.18 (corrected on 8.20.18)
Thomas Dydek Educational Report_FINAL (4-9-2018)
Thomas Dydek MDL Educational Report Dated 4.9.18

OTHER SOURCES:

American Cancer Society Ovarian Cancer Statistics
ATSDR Toxicological Profile for Asbestos
EPA Chemical Assessment Summary for Asbestos - 2017
EPA Guidelines for Carcinogen Risk Assessment - March 2005
EPA Health Assessment Document for Talc - 1992
Exhibit 1 - ATTORNEYS' EYES ONLY
Exhibit 2 - ATTORNEYS' EYES ONLY
Exhibit 3 - ATTORNEYS' EYES ONLY
FDA 4-1-2014 Response Letter to Epstein Denying Petition
Fitzgerald Analysis of J&J Baby Powder #1 and #2 Dated July 26, 2017
IARC Monograph 100C - Arsenic, Metals, Fibres, and Dusts - Excerpts
IARC Monograph 14 - Asbestos - 1977

IARC Monograph 2 - Some Inorganic and Organometallic Compounds - 1973
IARC Monograph 68 - Silica, Some Silicates, Coal Dust and Para-Aramid Fibrils - 1997
IARC Monograph 74 - Surgical Implants and Other Foreign Bodies - 1999
IARC Monograph 82 - Some Traditional Herbal Medicines, Some Mycotoxins, Naphthalene and Styrene - 2002
IARC Monograph 86 - Cobalt in Hard Minerals and Cobalt Sulfate, Gallium Arsenide, Indium Phosphide and Vanadium Pentoxide - 2006
IARC Monograph 87 - Inorganic and Organic Lead Compounds – 2006

IMERYS013188	J&J History
IMERYS045182	J&J S2s and BP Product Analysis - 1972
IMERYS045184	JNJ 000087928
IMERYS048311	JNJ 000088570
IMERYS051370	JNJ 000285351
IMERYS053387	JNJ000025132
IMERYS090653	JNJ000062359
IMERYS098115	JNJ000062436
IMERYS105215	JNJ000063608
IMERYS210136	JNJ000063951
IMERYS210729	JNJ000064544
IMERYS219720	JNJ000064762; JNJ000265171
IMERYS286445	JNJ000065264
IMERYS304036	JNJ000065601
IMERYS340454	JNJ000087710
IMERYS340798	JNJ000087716
IMERYS342524	JNJ000089413
IMERYS406170	JNJ000231304
IMERYS422289	JNJ000237076
IMERYS 088907	JNJ000237379
IMERYS 284935	JNJ000239723
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IMERYS209971	JNJ000245002
IMERYS241866	JNJ000246437
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IMERYS279968	JNJ000347962
IMERYS281335	JNJ000347962
IMERYS281776	JNJ000521616
IMERYS324700	JNJ000000704
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IMERYS-A_0015663	JNJ000016645

JNJ000019415

JNJ000025132

JNJ000026987

JNJ000046293

JNJ000245678

JNJ000245762

JNJ000251888

JNJ000260700

JNJ000261010

JNJ000265536

JNJ000279507

JNJ000348778

JNJ000404860

PCPC_MDL00062175

Pltf_MISC_00000272 (JANSSEN-000001-19)

NIOSH Occupation Respiratory Diseases September 1986

NIOSH Preliminary Report on Fiber Exposure During Use of Baby Powders - 1972

NTP Technical Report on the Toxicology and Carcinogenesis Studies of Talc (CAS No. 14807-96-6)- 1993

NTP Toxicology and Carcinogenesis Studies of Talc in F344/N Rats and B6C3F Mice Report No. 421

P-468

Read-the-Letter-from-the-FDA-on-Cosmetics

The Birth of Our Baby Products _ Kilmer House

WCD 002478 - Exhibit 32 Waldstreicher

JNJ000460665

JNJ000526750

JNJ000886067

JNJAZ55_000000577

JNJAZ55_000000905

JNJAZ55_000004563

JNJAZ55_000008177

JNJL61_000014431

JNJMX68_000003728

JNJMX68_000012858

JNJMX68_000013019

JNJNL61_000079334

Arch Carson, MD, PhD Legal Testimony, 2015-2018

Elaine Hale and Kenneth Dorsey parker, Jr. v. Centerpoint Energy Houston Electric, LLC; in the 55th
District Court of Harris County, Texas.

2016 Harris County, TX for Plaintiff

Danny Henderson and Linda Henderson; Magdaleno Flores and Maria Flores; Shari Waldrop; and Bryan
Thomas v. Magnablend, Inc., Nugreen Specialty, Inc., Nugreen Solutions, Inc., and Enviro Tech Inc.; in
the 40th District Court of Ellis County, Texas.

2015 Ellis County, TX for Defendant

Edgar Guadalupe Solis v. Eastman Chemical Company, Texas Operations, Tradebe Environmental
Services, Inc. d/b/a Tradebe Industrial Services LLC; in the 234th District Court of Harris County, Texas.

2015 Harris County, TX for Defendant

Arch I. Carson, MD, PhD
Professional Consultation Fee Schedule

Evidence-base research, report preparation, documentation, conference	\$450/hr
Interview, physical examination or medical testing of patients	450/hr
Review of documents	450/hr
Testimony at deposition or trial plus expenses	450/hr
Inspection, examination or sampling of physical evidence or sites	450/hr
Travel (Travel maximum \$4,000 per diem, plus expenses)	200/hr
Laboratory analyses/studies	at cost
Overhead and Supplies	at cost

Exhibit 36

Molecular Basis Supporting the Association of Talcum Powder Use With Increased Risk of Ovarian Cancer

Reproductive Sciences
1-10

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Rong Fan, MS¹, Robert T. Morris, MD², and Ghassan M. Saed, PhD^{1,2}

Abstract

Genital use of talcum powder and its associated risk of ovarian cancer is an important controversial topic. Epithelial ovarian cancer (EOC) cells are known to manifest a persistent prooxidant state. Here we demonstrated that talc induces significant changes in key redox enzymes and enhances the prooxidant state in normal and EOC cells. Using real-time reverse transcription polymerase chain reaction and enzyme-linked immunosorbent assay, levels of CA-125, caspase-3, nitrate/nitrite, and selected key redox enzymes, including myeloperoxidase (MPO), inducible nitric oxide synthase (iNOS), superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX), and glutathione reductase (GSR), were determined. TaqMan genotype analysis utilizing the QuantStudio 12K Flex was used to assess single-nucleotide polymorphisms in genes corresponding to target enzymes. Cell proliferation was determined by MTT proliferation assay. In all talc-treated cells, there was a significant dose-dependent increase in prooxidant iNOS, nitrate/nitrite, and MPO with a concomitant decrease in antioxidants CAT, SOD, GSR, and GPX ($P < .05$). Remarkably, talc exposure induced specific point mutations that are known to alter the activity in some of these key enzymes. Talc exposure also resulted in a significant increase in inflammation as determined by increased tumor marker CA-125 ($P < .05$). More importantly, talc exposure significantly induced cell proliferation and decreased apoptosis in cancer cells and to a greater degree in normal cells ($P < .05$). These findings are the first to confirm the cellular effect of talc and provide a molecular mechanism to previous reports linking genital use to increased ovarian cancer risk.

Keywords

talc, epithelial ovarian cancer, oxidative stress, single-nucleotide polymorphism, cell proliferation

Introduction

Ovarian cancer is the most lethal gynecologic malignancy and ranks fifth in cancer deaths among women diagnosed with cancer.¹ Epithelial ovarian cancer (EOC) has long been considered a heterogeneous disease with respect to histopathology, molecular biology, and clinical outcome.^{1,2} Although surgical techniques and treatments have advanced over the years, the prognosis of EOC remains poor, with a 5-year survival rate of 50% in advanced stage.² This is largely due to the lack of early warning symptoms and screening methods and the development of chemoresistance.^{1,2} Moreover, ovarian cancer is known to be associated with germline mutations in the *BRCA1* or *BRCA2* genes, but with a rate of only 20 % to 40%, suggesting the presence of other unknown mutations in other predisposition genes.³ Additional genetic variations including single-nucleotide polymorphisms (SNPs) have been hypothesized to act as low to moderate penetrant alleles that contribute to ovarian cancer risk.^{3,4}

The pathophysiology of EOC is not fully understood but has been strongly associated with inflammation and the resultant

oxidative stress.⁵ We have previously characterized EOC cells to manifest a persistent prooxidant state as evident by the upregulation of key oxidants and downregulation of key antioxidants, which is further enhanced in chemoresistant EOC cells.⁶ The expression of key prooxidant/inflammatory enzymes such as inducible nitric oxide synthase (iNOS), nicotinamide adenine dinucleotide phosphate (NAD(P)H) oxidase, and myeloperoxidase (MPO), as well as an increase in nitric oxide (NO) levels, was increased in EOC tissues and cells.⁶ Additionally, we have shown that EOC cells manifest lower apoptosis, which

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was markedly induced by inhibiting iNOS, indicating a strong link between apoptosis and NO/iNOS pathways in these cells.⁶

The cellular redox balance is maintained by key antioxidants including catalase (CAT), superoxide dismutase (SOD), or by glutathione peroxidase (GPX) coupled with glutathione reductase (GSR).⁵ Other important scavengers include thioredoxin coupled with thioredoxin reductase, and glutaredoxin, which utilizes glutathione (GSH) as a substrate.⁷ We have previously reported that a genotype switch in key antioxidants is a potential mechanism leading to the acquisition of chemoresistance in EOC cells.⁷ We have studied the effects of genetic polymorphisms in key redox genes on the acquisition of the oncogenic phenotype in EOC cells, including genes that control the levels of cellular reactive oxygen species and oxidative damage and SNPs for genes involved in carcinogen metabolism (detoxification and/or activation), antioxidants, and DNA repair pathways.^{4,6} Several function-altering SNPs have been identified in key antioxidants, including CAT, GPX, GSR, and SOD.⁴

Several studies have suggested the possible association between genital use of talcum powder and risk of EOC.⁷⁻¹² Association between the use of cosmetic talc in genital hygiene and ovarian cancer was first described in 1982 by Cramer et al, and many subsequent studies supported this finding.⁷⁻¹² Talc and asbestos are both silicate minerals; the carcinogenic effects of asbestos have been extensively studied and documented in the medical literature.⁷⁻¹² Asbestos fibers in the lung initiate an inflammatory and scarring process, and it has been proposed that ground talc, as a foreign body, might initiate a similar inflammatory response.⁷ The objective of this study was to determine the effects of talcum powder on the expression of key redox enzymes, CA-125 levels, and cell proliferation and apoptosis in normal and EOC cells.

Material and Methods

Cell Lines

Ovarian cancer cells SKOV-3 (ATCC), A2780 (Sigma Aldrich, St Louis, Missouri), and TOV112D (a kind gift from Gen Sheng Wu at Wayne State University, Detroit, Michigan) and normal cells human macrophages (EL-1; ATCC, Manassas, Virginia), human primary normal ovarian epithelial cells (Cell Biologics, Chicago, Illinois), human ovarian epithelial cells (HOSEpiC; ScienCell Research Laboratories, Inc, Carlsbad, California), and immortalized human fallopian tube secretory epithelial cells (FT33; Applied Biological Materials, Richmond, British Columbia, Canada) were used. All cells were grown in media and conditions following manufacturer's protocol. EL-1 cells were grown in IMDM media (ATCC) supplemented with 0.1 mM hypoxanthine and 0.1 mM thymidine solution (H-T, ATCC) and 0.05 mM β -mercaptoethanol. SKOV-3 EOC cells were grown in HyClone McCoy's 5A medium (Fisher Scientific, Waltham, Massachusetts), A2780 EOC cells were grown in HyClone RPMI-1640 (Fisher Scientific), and both TOV112D EOC cells were grown in MCDB105

(Cell Applications, San Diego, California) and Medium 199 (Fisher Scientific; 1:1). All media were supplemented with fetal bovine serum (Innovative Research, Novi, Michigan) and penicillin/streptomycin (Fisher Scientific), per their manufacturer specifications. Human primary normal ovarian epithelial cells were grown in complete human epithelial cell medium (Cell Biologics).

Treatment of Cells

Talcum baby powder (Johnson & Johnson, New Brunswick, NJ, #30027477, Lot#13717RA) was dissolved in dimethyl sulfoxide (DMSO; Sigma Aldrich) at a concentration of 500 mg in 10 mL and was filtered with a 0.2 μ m syringe filter (Corning). Sterile DMSO was used as a control for all treatments. Cells were seeded in 100-mm cell culture dishes (3×10^6) and were treated 24 hours later with 5, 20, or 100 μ g/mL of talc for 72 hours. Cell pellets were collected for RNA, DNA, and protein extraction. Cell culture media were collected for CA-125 analysis by enzyme-linked immunosorbent assay (ELISA).

Real-Time Reverse Transcription Polymerase Chain Reaction

Total RNA was extracted from all cells using the RNeasy mini kit (Qiagen, Valencia, California). Measurement of the amount of RNA in each sample was performed using a Nanodrop spectrophotometer (Thermo Fisher Scientific, Waltham, Massachusetts). A 20 μ L complementary DNA reaction volume containing 0.5 μ g RNA was prepared using the SuperScript VILO Master Mix Kit (Life Technologies, Carlsbad, California). Optimal oligonucleotide primer pairs were selected for each target using Beacon designer (Premier Biosoft, Inc; Table 1). Quantitative reverse transcription polymerase chain reaction (RT-PCR) was performed using the EXPRESS SYBR GreenER qPCR supermix kit (Life Technologies) and the Cepheid 1.2f detection system (Sunnyvale, CA) previously described.⁶ Standards with known concentrations and lengths were designed specifically for β -actin (79 bp), CAT (105 bp), NOS2 (89 bp), GSR (103 bp), GPX1 (100 bp), MPO (79 bp), and SOD3 (84 bp), allowing for construction of a standard curve using a 10-fold dilution series.⁶ All samples were normalized to β -actin. A final melting curve analysis was performed to demonstrate specificity of the PCR product.

Protein Detection

Cell pellets were lysed utilizing cell lysis buffer (20 mM Tris-HCl [pH 7.5], 150 mM NaCl, 1 mM Na₂EDTA, 1 mM EGTA, 1% Triton, 2.5 sodium pyrophosphate, 1 mM β -glycerophosphate, 1 mM Na₃VO₄, 1 μ g/mL leupeptin) containing a cocktail of protease inhibitors. Samples were centrifuged at 13 000 rpm for 10 minutes at 4°C. Total protein concentration of cell lysates from control and talc-treated cells was measured with the Pierce BCA protein assay kit (Thermo Scientific, Rockford, Illinois).

Table 1. Real-Time RT-PCR Oligonucleotide Primers.

Accession Number	Gene	Sense (5'-3')	Antisense (3'-5')	Amplicon (bp)	Annealing Time (seconds) and Temperature (°C)
NM_001101	<i>β-actin</i>	ATGACTTAGTTGCGTTACAC	AATAAAGCCATGCCAATCTC	79	10, 64
NM_001752	<i>CAT</i>	GGTTGAACAGATAGCCTTC	CGGTGAGTGTGAGGATAG	105	10, 63
NM_003102	<i>SOD3</i>	GTGTTCCCTGCCTGCTCCT	TCCGCCGAGTCAGAGTTG	84	60, 64
NM_000637	<i>GSR</i>	TCACCAAGTCCCATATAGAAATC	TGTGGCGATCAGGATGTG	116	10, 63
NM_000581	<i>GPX1</i>	GGACTACACCCAGATGAAC	GAGCCCTTGCGAGGTGTAG	91	10, 66
NM_000625	<i>NOS2</i>	GAGGACCACATCTACCAAGGAGGAG	CCAGGCAGGCGGAATAGG	89	30, 59
NM_000250	<i>MPO</i>	CACTTGTATCCTCTGGTTCTTCAT	TCTATATGCTTCTCACGCCTAGTA	79	60, 63

Abbreviation: RT-PCR, reverse transcription polymerase chain reaction.

Detection of Protein/Activity by ELISA

The following ELISA kits were used (Cayman Chemical, Ann Arbor, Michigan): CAT, SOD, GSR, GPX, and MPO. Nitrite (NO_2^-)/nitrate (NO_3^-) were determined spectrophotometrically by Griess assay as previously reported.⁶ CA-125 protein levels were measured in cell media by ELISA (Ray Biotech, Norcross, Georgia).

TaqMan SNP Genotyping Assay

DNA was isolated utilizing the EZ1 DNA tissue kit (Qiagen) for EOC cells. The TaqMan SNP genotyping assay set (Applied Biosystems, Carlsbad, California; NCBI dbSNP genome build 37, MAF source 1000 genomes) was used to genotype the SNPs (Table 1). The Applied Genomics Technology Center (AGTC, Wayne State University) performed these assays. Analysis was done utilizing the QuantStudio 12 K Flex real-time PCR system (Applied Biosystems).

Cell Proliferation and Apoptosis

Cell proliferation was assessed with the TACS MTT cell proliferation assay (Trevigen, Gaithersburg, Maryland) after treatment with talc (100 $\mu\text{g/mL}$) for 24 hours. The Caspase-3 Colorimetric Activity Assay Kit (Chemicon, Temecula, California) was used to determine levels of caspase-3 activity after treatment of normal and EOC cells with various doses of talc as previously described.⁶ Equal concentrations of cell lysate were used. The assay is based on spectrophotometric detection of the chromophore p-nitroaniline (pNA) after cleavage from the labeled substrate DEVD-pNA. The free pNA can be quantified using a spectrophotometer or a microtiter plate reader at 405 nm. Comparison of the absorbance of pNA from an apoptotic sample with its control allows determination of the percentage increase in caspase-3 activity.

Statistical Analysis

Normality was examined using the Kolmogorov-Smirnov test and by visual inspection of quantile-quantile plots. Because most of the data were not normally distributed, differences in distributions were examined using the Kruskal-Wallis test.

Generalized linear models were fit to examine pairwise differences in estimated least squares mean expression values by exposure to 0, 5, 20, or 100 $\mu\text{g/mL}$ of talc. We used the Tukey-Kramer adjustment for multiple comparisons, and the regression models were fit using log2 transformed analyte expression values after adding a numeric constant “1” to meet model assumptions while avoiding negative transformed values. *P* values below .05 are statistically significant.

Results

Talc Treatment Decreased the Expression of Antioxidant Enzymes SOD and CAT in Normal and EOC Cells

Real-time RT-PCR and ELISA assays were utilized to determine the CAT and SOD messenger RNA (mRNA) and protein levels in cells before and after 72 hours talc treatment, respectively (Figure 1). The CAT (Figure 1A and C) and SOD (Figure 1B and D) mRNA and protein levels were significantly decreased in a dose-dependent manner in talc-treated cells compared to controls ($P < .05$).

Talc Treatment Increased the Expression of Prooxidants iNOS, $\text{NO}_2^-/\text{NO}_3^-$, and MPO in Normal and EOC Cells

Real-time RT-PCR and $\text{NO}_2^-/\text{NO}_3^-$ assays were utilized to determine the iNOS mRNA and NO levels in cells before and after 72 hours talc treatment, respectively (Figure 2). The iNOS mRNA and NO levels were significantly increased in a dose-dependent manner in talc-treated cells as compared to their controls (Figure 2A and C, $P < .05$). As expected, there was no detectable MPO in normal ovarian and fallopian tube cells, and thus, talc treatment did not have any effect. However, MPO mRNA and protein levels were significantly increased in a dose-dependent manner in talc-treated ovarian cancer cells and macrophages compared to controls (Figure 2B and D, $P < .05$).

Talc Treatment Decreased the Expression of Antioxidant Enzymes, GPX and GSR, in Normal and EOC Cells

Real-time RT-PCR and ELISA assays were utilized to determine the GPX and GSR mRNA and protein levels in cells before and

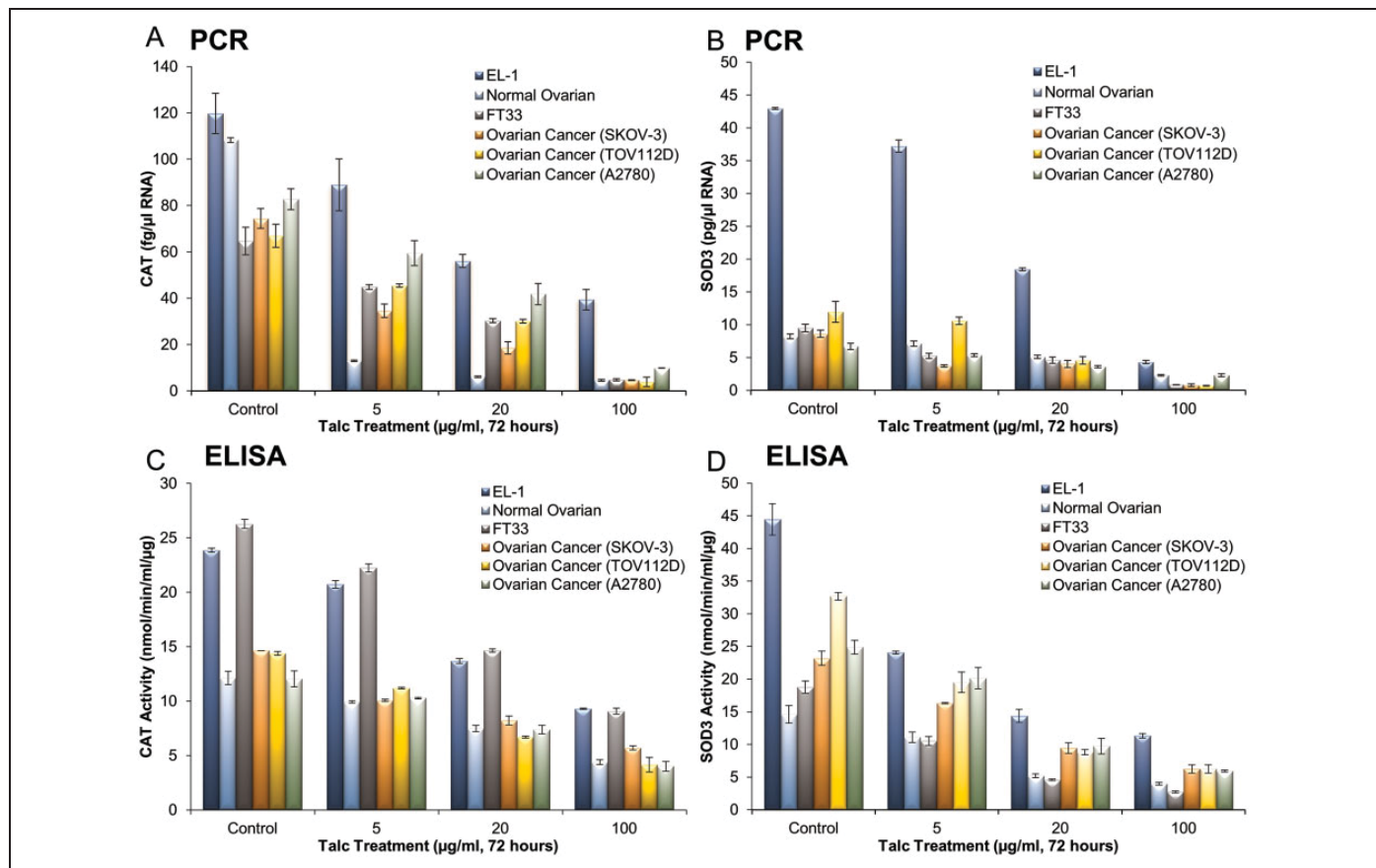


Figure 1. Decreased expression and activity of key antioxidant enzymes, CAT and SOD3. The mRNA (real-time RT-PCR) and protein/activity levels (ELISA) of CAT (A and C) and SOD3 (B and D) were determined in macrophages (EL-1), human primary ovarian epithelial cells (normal ovarian), fallopian tube (FT33), and ovarian cancer (SKOV-3, TOV112D, and A2780) cell lines before and after treatment with various doses of talc over 72 hours. Experiments were performed in triplicate. Expression is depicted as the mean, with error bars representing standard deviation. All changes in response to talc treatment were significant ($P < .05$) in all cells and in all doses as compared to controls. CAT indicates catalase; SOD3, superoxide dismutase 3; mRNA, messenger RNA; RT-PCR, reverse transcription polymerase chain reaction; ELISA, enzyme-linked immunosorbent assay.

after 72 hours of talc treatment, respectively (Figure 3). The GPX (Figure 3A and C) and GSR (Figure 3B and D) mRNA and protein levels were significantly decreased in a dose-dependent manner in talc-treated cells compared to controls ($P < .05$).

Talc Exposure Induced Known Genotype Switches in Key Oxidant and Antioxidant Enzymes

Talc treatment was associated with a genotype switch in *NOS2* from the common C/C genotype in untreated cells to T/T, the SNP genotype, in talc-treated cells, except in A2780 and TOV112D (Table 2). Additionally, the observed decrease in CAT expression and activity was associated with a genotype switch from common C/C genotype in CAT in untreated cells to C/T, the SNP genotype, in TOV112D and all normal talc-treated cells. However, there was no detectable genotype switch in CAT in A2780, SKOV3, and TOV112D (Table 2). Remarkably, there was no observed genotype switch in the selected SNP for SOD3 and GSR in all talc-treated cells. All cells, except for HOSEpiC cells, manifest the SNP genotype of

GPX1 (C/T). Intriguingly, talc treatment reversed this SNP genotype to the normal genotype (Table 2).

Talc Treatment Increased CA-125 Levels in Normal and EOC Cells

CA-125 ELISA assay was performed in protein isolated from cell media before and after talc treatment. CA-125 levels were significantly increased in a dose-dependent manner in all cells (Figure 4, $P < .05$). There was no detectable CA-125 protein in macrophages.

Talc Treatment Increased Cell Proliferation and Decreased Apoptosis

MTT cell proliferation assay was used to determine cell viability, and caspase-3 activity assay was utilized to determine apoptosis of all cell lines after 24 hours of talc treatment (Figure 5). Cell proliferation was significantly increased from the baseline in all talc-treated cells ($P < .05$), but to a greater degree in normal

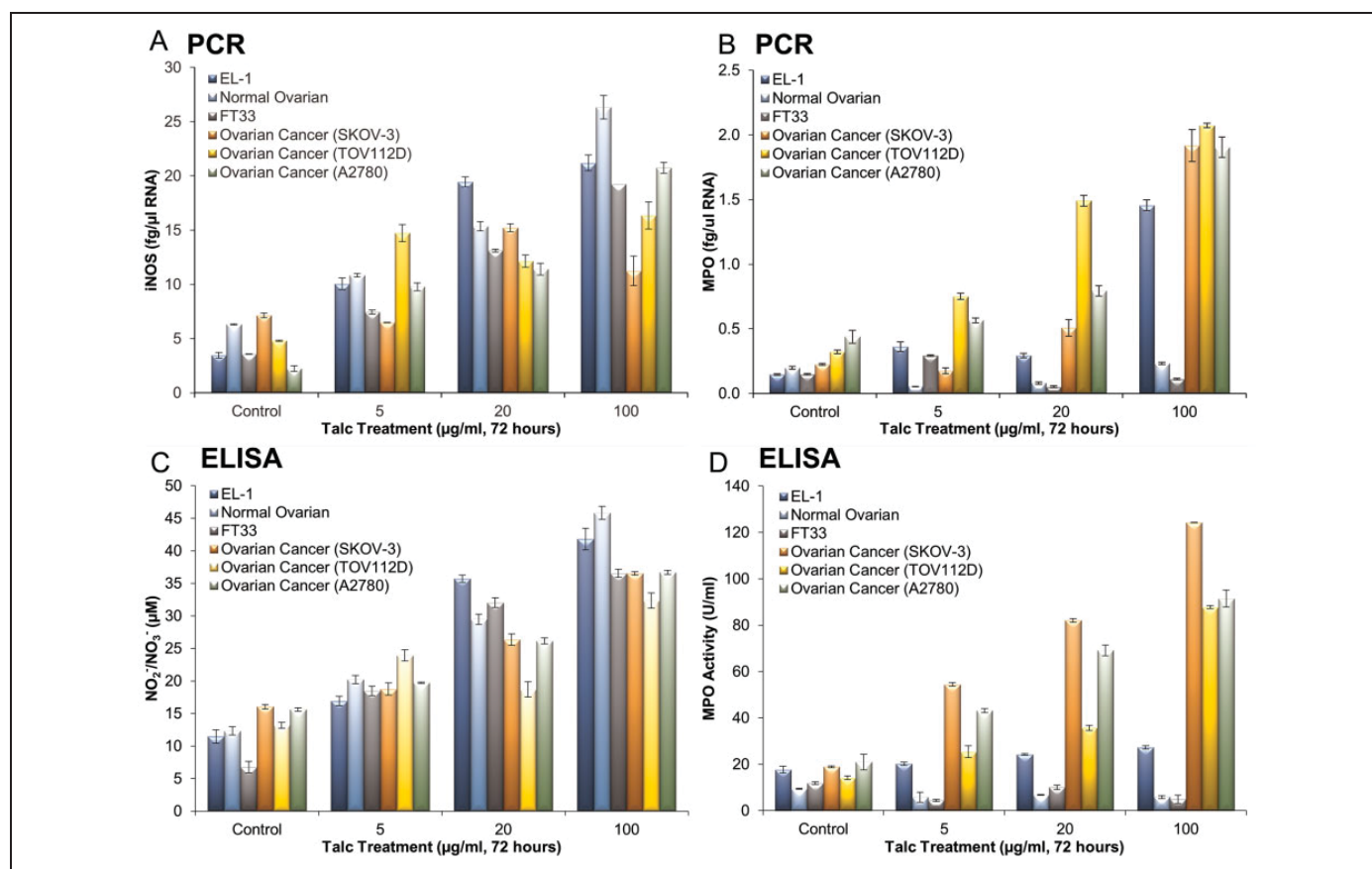


Figure 2. Increased expression and activity of key prooxidants, iNOS, NO₂⁻/NO₃⁻, and MPO. The mRNA (real-time RT-PCR) and protein/activity levels (ELISA) of iNOS (A and C) and MPO (B and D) were determined in macrophages (EL-1), human primary ovarian epithelial cells (normal ovarian), fallopian tube (FT33), and ovarian cancer (SKOV-3, TOV112D, and A2780) cell lines before and after treatment with various doses of talc over 72 hours. As expected, there was no detectable MPO in normal ovarian and fallopian tube cells, and thus, talc treatment did not have any effect. Experiments were performed in triplicate. Expression is depicted as the mean, with error bars representing standard deviation. All changes in response to talc treatment were significant ($P < .05$) in iNOS and MPO-positive cells and in all doses as compared to controls. iNOS indicates inducible nitric oxide synthase; MPO, myeloperoxidase; mRNA, messenger RNA; RT-PCR, reverse transcription polymerase chain reaction; ELISA, enzyme-linked immunosorbent assay.

as compared to cancer cells. As anticipated, caspase-3 was significantly reduced in cancer as compared to normal cells. Talc treatment resulted in decreased caspase-3 activity in all cells as compared to controls (Figure 6, $P < .05$), indicating a decrease in apoptosis.

Discussion

The claim that regular use of talcum powder for hygiene purpose is associated with an increased risk of ovarian cancer is based on several reports confirming the presence of talc particles in the ovaries and other parts of the female reproductive tract as well as in lymphatic vessels and tissues of the pelvis.⁷⁻¹² The ability of talc particles to migrate through the genital tract to the distal fallopian tube and ovaries is well accepted.¹⁰ To date, the exact mechanism is not fully understood, though several studies have pointed toward the peristaltic pump feature of the uterus and fallopian tubes, which is known to enhance transport of sperm into the oviduct ipsilateral to the ovary bearing the dominant follicle.⁸⁻¹²

There are reports supporting the epidemiologic association of talc use and risk of ovarian cancer.^{11,12} Recent studies have shown that risks for EOC from genital talc use vary by histologic subtype, menopausal status at diagnosis, hormone therapy use, weight, and smoking. These observations suggest that estrogen and/or prolactin may play a role via macrophage activity and inflammatory response to talc. There has been debate as to the significance of the epidemiologic studies based on the fact that the reported epidemiologic risk of talc use and risk of ovarian cancer, although consistent, are relatively modest (30%-40%), and there is inconsistent increase in risk with duration of use. This observation is due, in part, to the challenges in quantifying exposure as well as the failure of epidemiological studies to obtain necessary information about the frequency and duration of usage.¹¹⁻¹³

In this study, we have shown beyond doubt that talc alters key redox and inflammatory markers, enhances cell proliferation, and inhibits apoptosis, which are hallmarks of ovarian cancer. More importantly, this effect is also manifested by talc in normal cells, including surface ovarian epithelium,

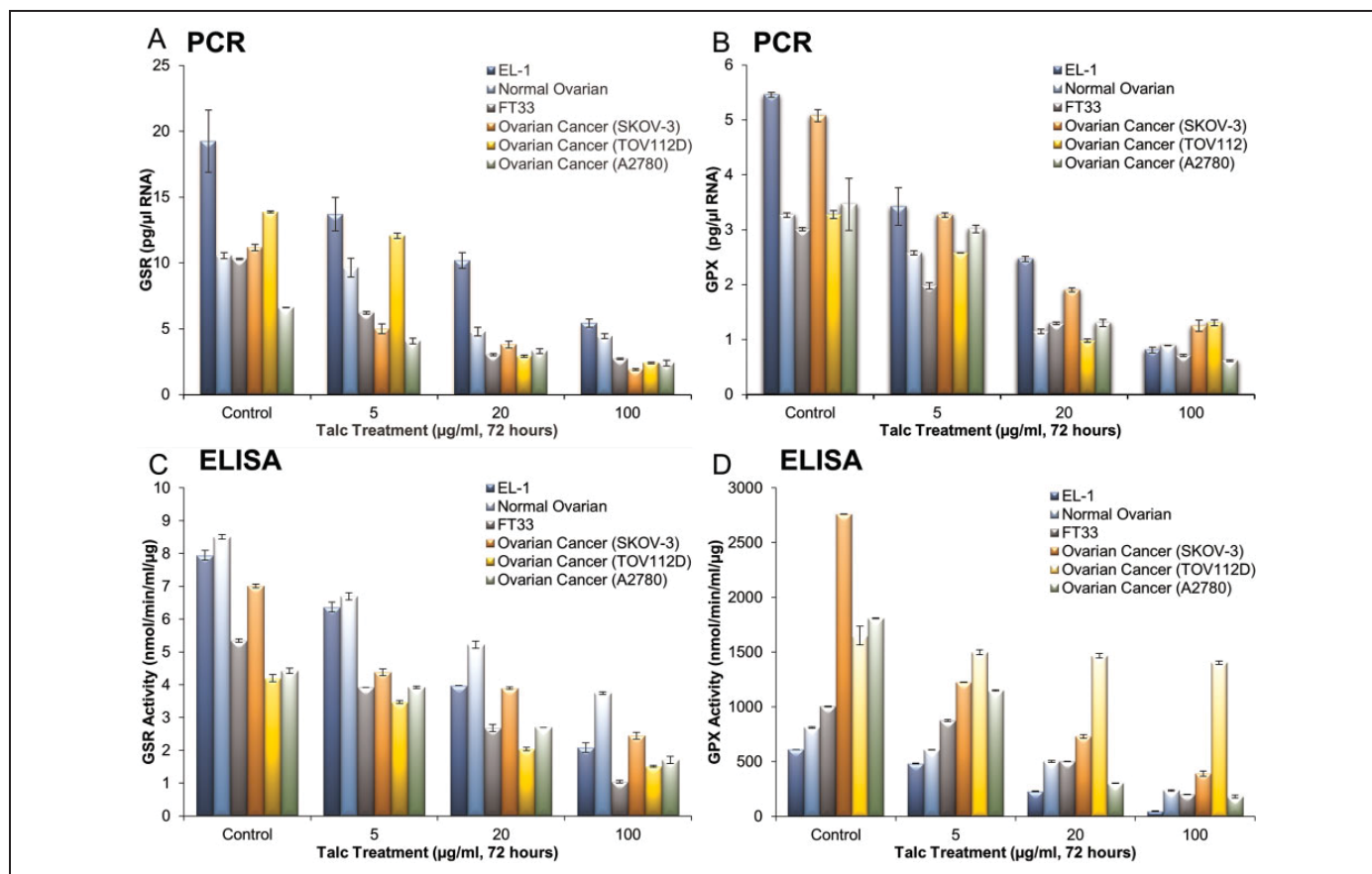


Figure 3. Decreased expression and activity of key antioxidant enzymes, GSR and GPX. The mRNA (real-time RT-PCR) and protein/activity levels (ELISA) of GSR (A and C) and GPX (B and D) were determined in macrophages (EL-1), human primary ovarian epithelial cells (normal ovarian), fallopian tube (FT33), and ovarian cancer (SKOV-3, TOV112D, and A2780) cell lines before and after treatment with various doses of talc over 72 hours. Experiments were performed in triplicate. Expression is depicted as the mean, with error bars representing standard deviation. All changes in response to talc treatment were significant ($P < .05$) in all cells and in all doses as compared to controls. GSR indicates glutathione reductase; GPX, glutathione peroxidase; mRNA, messenger RNA; RT-PCR, reverse transcription polymerase chain reaction; ELISA, enzyme-linked immunosorbent assay.

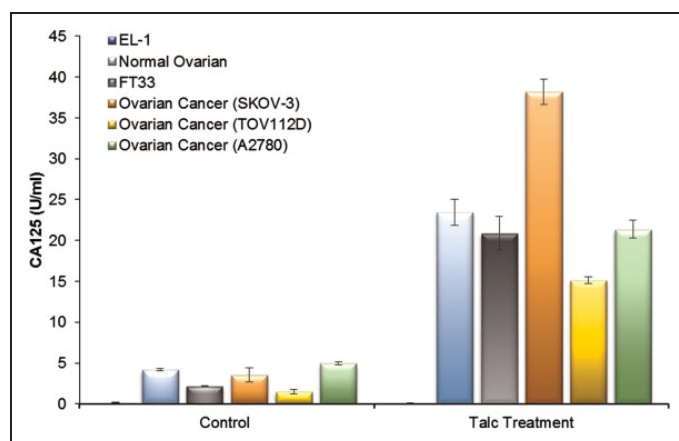
fallopian tube, and macrophages. Oxidative stress has been implicated in the pathogenesis of ovarian cancer, specifically by increased expression of several key prooxidant enzymes such as iNOS, MPO, and NAD(P)H oxidase in EOC tissues and cells as compared to normal cells indicating an enhanced redox state, as we have recently demonstrated (Figure 7).⁶ This redox state is further enhanced in chemoresistant EOC cells as evident by a further increase in iNOS and $\text{NO}_2^-/\text{NO}_3^-$ and a decrease in GSR levels, suggesting a shift toward a prooxidant state.⁶ Antioxidant enzymes, key regulators of cellular redox balance, are differentially expressed in various cancers, including ovarian.^{6,14} Specifically, GPX expression is reduced in prostate, bladder, kidney, and estrogen receptor negative breast cancer cell lines, though GPX is increased in other cancerous tissues from breast.¹⁴ Glutathione reductase levels, on the other hand, are elevated in lung cancer, although differentially expressed in breast and kidney cancer.^{5,15} Similarly, CAT was decreased in breast, bladder, and lung cancer while increased in brain cancer.¹⁶⁻¹⁸ Superoxide dismutase is expressed in lung, colorectal, gastric ovarian, and breast

cancer, while decreased activity and expression have been reported in colorectal carcinomas and pancreatic cancer cells.¹⁸⁻²¹ Collectively, this differential expression of antioxidants demonstrates the unique and complex redox microenvironment in cancer. Glutathione reductase is a flavoprotein that catalyzes the NADPH-dependent reduction of oxidized glutathione (GSSG) to GSH. This enzyme is essential for the GSH redox cycle that maintains adequate levels of reduced cellular GSH. A high GSH to GSSG ratio is essential for protection against oxidative stress (Figure 5). Treatment with talc significantly reduced GSR in normal and cancer cells, altering the redox balance (Figure 3A and C). Likewise, GPX is an enzyme that detoxifies reactive electrophilic intermediates and thus plays an important role in protecting cells from cytotoxic and carcinogenic agents. Overexpression of GPX is triggered by exogenous chemical agents and reactive oxygen species and is thus thought to represent an adaptive response to stress.¹⁵ Indeed, treatment of normal and cancer cells with talc significantly reduced GPX, which compromised the overall cell response to stress (Figure 3B and D).

Table 2. SNP Characteristics (A) and SNP Genotyping of Key Redox Enzymes in Untreated and Talc-Treated (100 µg/mL) Human Primary Ovarian Epithelial Cells (Normal Ovarian), Human Ovarian Surface Epithelial Cells (HOSEpiC), Fallopian Tube (FT33), and Ovarian Cancer (A2780, SKOV-3, TOV112D) Cell Lines (B).

	Gene (rs Number)				
	CAT (rs769217)	NOS ₂ (rs2297518)	GSR (rs8190955)	GPX1 (rs3448)	SOD3 (rs2536512)
A					
MAF	0.123	0.173	0.191	0.176	0.476
SNP	C-262T	C2087T	G201T	C-1040T	A377T
Chromosome location	11p13	17q11.2	8p12	3q21.31	4p15.2
Amino acid switch	Isoleucine to Threonine	Serine to Leucine	Unknown	Unknown	Alanine to threonine
Effect on activity	Decrease	Increase	Unknown	Unknown	Decrease
B					
A2780: Control	C/C	C/C	G/G	C/T	A/A
A2780: Talc	C/C	C/C	G/G	C/C	A/A
SKOV-3: Control	C/C	C/C	G/G	C/T	A/A
SKOV-3: Talc	C/C	T/T	G/G	C/C	A/A
TOV112D: Control	C/C	C/C	G/G	C/T	A/A
TOV112D: Talc	C/T	C/C	G/G	C/C	A/A
HOSEpiC: Control	C/C	C/C	G/G	C/T	A/A
HOSEpiC: Talc	C/T	T/T	G/G	C/T	A/A
FT33: Control	C/C	C/C	G/G	C/T	A/A
FT33: Talc	C/T	T/T	G/G	C/C	A/A
Normal ovarian: Control	C/C	C/C	G/G	C/T	A/A
Normal ovarian: Talc	C/T	T/T	G/G	C/C	A/A

Abbreviation: SNP, single-nucleotide polymorphism.

**Figure 4.** Increased CA-125 levels in response to talc treatment. The level of ovarian cancer biomarker CA-125 was determined by ELISA before and after 72 hours of talc treatment (100 µg/mL) in macrophages (EL-1), human primary ovarian epithelial cells (normal ovarian), fallopian tube (FT33), and ovarian cancer (SKOV-3, TOV112D, and A2780) cells. Experiments were performed in triplicate. Expression is depicted as the mean, with error bars representing standard deviation. All changes in response to talc treatment were significant ($P < .05$) in all cells as compared to controls. ELISA indicates enzyme-linked immunosorbent assay.

We have previously reported that EOC cells manifest increased cell proliferations and decreased apoptosis.⁶ In this study, we have shown that talc enhances cell proliferation and induces an inhibition in apoptosis in EOC cells, but more importantly in normal cells, suggesting talc is a stimulus to the development of the oncogenic phenotype. We also previously

reported a cross talk between iNOS and MPO in ovarian cancer, which contributed to the lower apoptosis observed in ovarian cancer cells.^{6,22} Myeloperoxidase, an abundant hemoprotein, previously known to be present solely in neutrophils and monocytes, is a key oxidant enzyme that utilizes NO produced by iNOS as a 1-electron substrate generating NO⁺, a labile nitrosylating species.^{6,23,24} We were the first to report that MPO was expressed by EOC cells and tissues and that silencing MPO gene expression utilizing MPO-specific siRNA induced apoptosis in EOC cells through a mechanism that involved the S-nitrosylation of caspase-3 by MPO.²² Additionally, we have compelling evidence that MPO serves as a source of free iron under oxidative stress, where both NO⁺ and superoxide are elevated.⁶ Iron reacts with hydrogen peroxide (H₂O₂) and catalyzes the generation of highly reactive hydroxy radical (HO•), thereby increasing oxidative stress, which in turn increases free iron concentrations by the Fenton and Haber-Weiss reaction.^{6,24} We have previously highlighted the potential benefits of the combination of serum MPO and free iron as biomarkers for early detection and prognosis of ovarian cancer.²⁵ Collectively, we now have substantial evidence demonstrating that altered oxidative stress may play a role in maintaining the oncogenic phenotype of EOC cells. Treatment of normal or ovarian cancer cells with talc resulted in a significant increase in MPO and iNOS, supporting the role of talc in the enhancement of a prooxidant state that is a major cause in the development and maintenance of the oncogenic phenotype (Figure 2).

Furthermore, CA-125, which exists as a membrane-bound and secreted protein in EOC cells, has been established as a

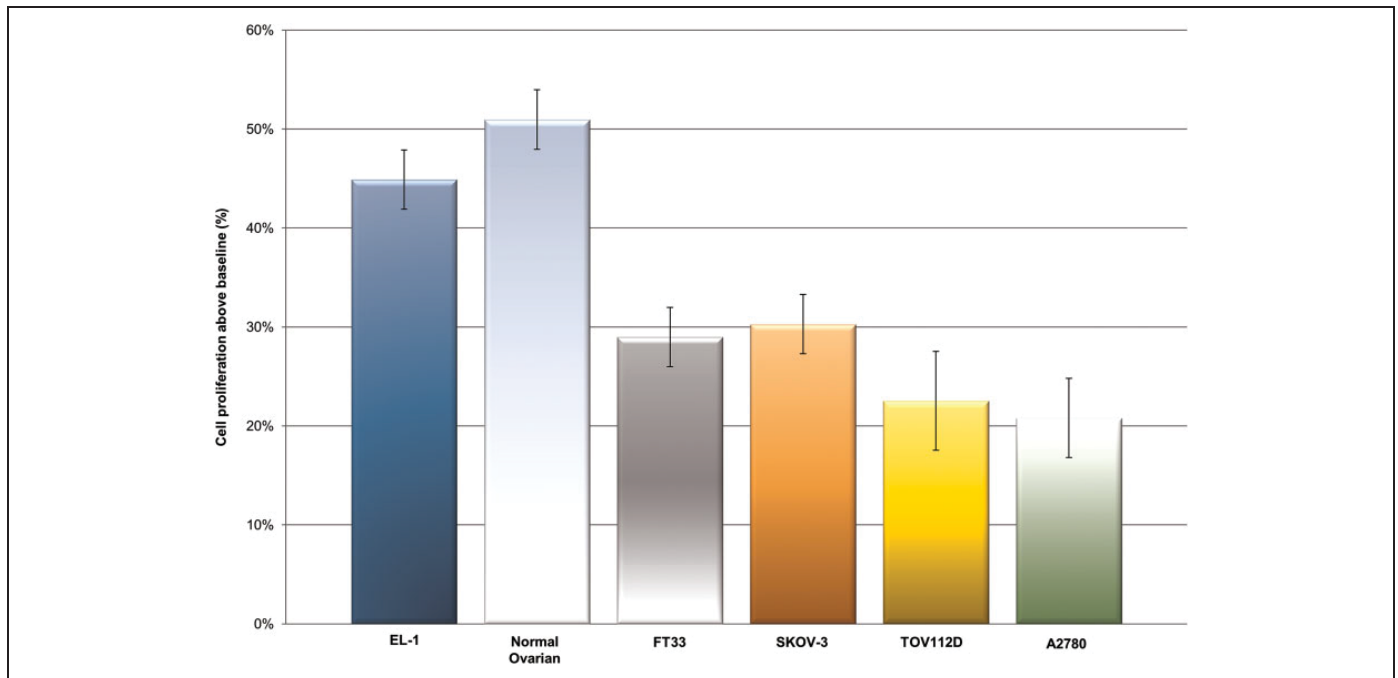


Figure 5. Increased cell proliferation in response to talc treatment. Cell proliferation was determined by MTT cell proliferation assay after 24 hours of talc treatment (100 µg/mL) in macrophages (EL-1), human primary ovarian epithelial cells (normal ovarian), fallopian tube (FT33), and ovarian cancer (SKOV-3, TOV112D, and A2780) cells. Experiments were performed in triplicate. Cell proliferation is depicted as the mean, with error bars representing standard deviation. All changes in response to talc treatment were significant ($P < .05$) in all cells as compared to controls.

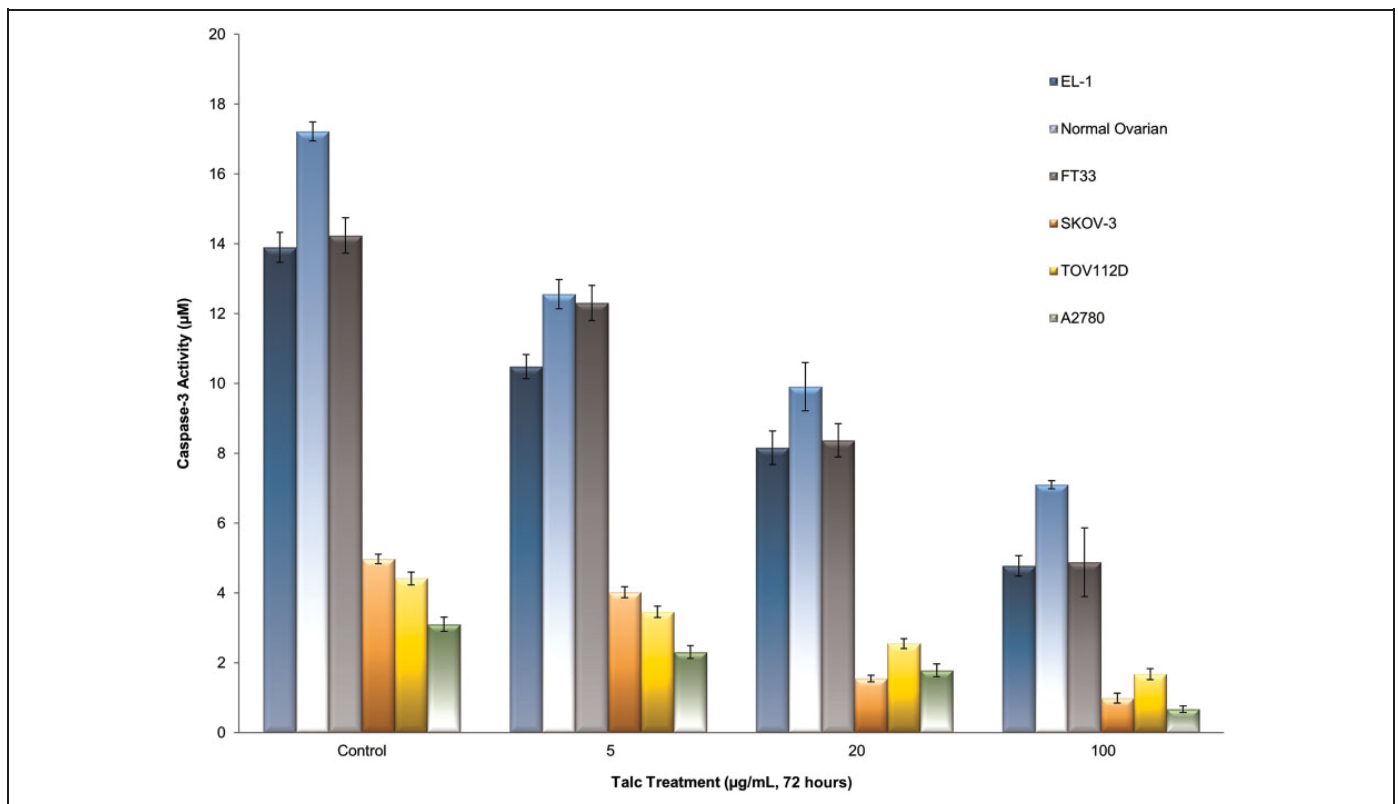


Figure 6. Decreased apoptosis in response to talc treatment. Caspase-3 activity was used to measure the degree of apoptosis in all cells. Caspase-3 activity assay was utilized to determine caspase-3 activity in macrophages (EL-1), human primary ovarian epithelial cells (normal ovarian), fallopian tube (FT33), and ovarian cancer (SKOV-3, TOV112D, and A2780) cell lines before and after treatment with various doses of talc over 72 hours. Experiments were performed in triplicate. Expression is depicted as the mean, with error bars representing standard error. All changes in response to talc treatment were significant ($P < .05$) in all cells and in all doses as compared to controls.

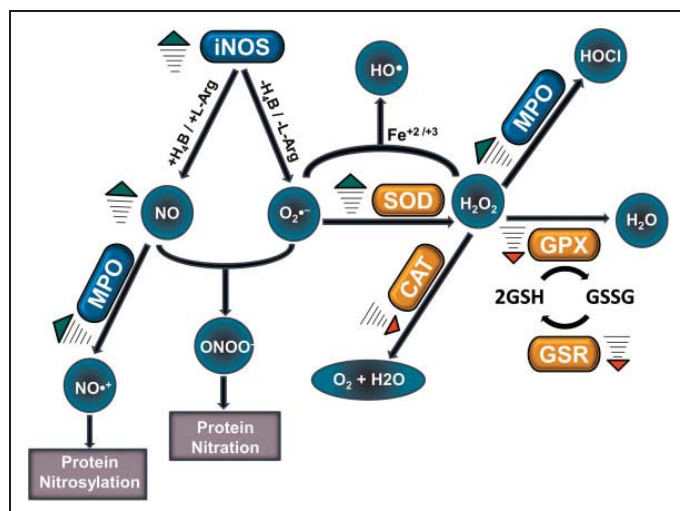


Figure 7. Epithelial ovarian cancer (EOC) cells have been reported to manifest a persistent prooxidant state as evident by the upregulation (green arrows) of key oxidants iNOS, NO, NO⁺, ONOO⁻, OH⁻, O₂⁺, and MPO (blue) and downregulation (red arrows) of key antioxidants SOD, CAT, GPX, and GSR (orange). This redox state was also shown to be further enhanced in chemoresistant EOC cells. In this study, talcum powder altered the redox state, as indicated by the arrows, of both normal and EOC cells to create an enhanced prooxidant state. iNOS indicates inducible nitric oxide synthase; MPO, myeloperoxidase; SOD, superoxide dismutase; CAT, catalase; GPX, glutathione peroxidase; GSR, glutathione reductase.

biomarker for disease progression and response to treatment.² CA-125 expression was significantly increased from nearly undetectable levels in controls to values approaching clinical significance (35 U/mL in postmenopausal women²⁶) in talc-treated cells (Figure 4, $P < .05$) without the physiologic effects on the tumor microenvironment one would expect to be present in the human body, thus highlighting the implications of the prooxidant states caused by talc alone.

To elucidate the mechanism by which talc alters the redox balance to favor a prooxidant state not only in ovarian cancer cells, but more importantly in normal cells, we have examined selected known gene mutations corresponding to SNPs known to be associated with altered enzymatic activity and increased cancer risk.^{6,27} Our results show that the *CAT* SNP (rs769217) resulting in decreased enzymatic activity was induced in all normal cell lines tested and in TOV112D EOC lines, but was not detected in A2780 or SKOV-3 cell lines (Table 2). Nevertheless, our results confirm a decrease in *CAT* expression and enzymatic activity in all talc-treated cells (Figure 1), indicating the existence of other *CAT* SNPs. The *SOD3* (rs2536512) and *GSR* (rs8190955) SNP genotypes were not detected in any cell line, yet *SOD3* and *GSR* activity and expression were decreased in all talc-treated cells, again suggesting the presence of other SNPs. Our results have also shown that all cells, except for HOSEpiC cells, manifest the SNP genotype of *GPX1* (C/T) before talc treatment. Intriguingly, talc treatment reversed this SNP genotype to the normal genotype (Table 2). Consistent with this finding, we have previously reported that acquisition

of chemoresistance by ovarian cancer cells is associated with a switch from the *GPX1* SNP genotype to the normal *GPX1* genotype.⁶ It is not understood why a *GPX1* SNP genotype predominates in untreated normal and ovarian cancer cells. Our results showed that talc treatment was associated with a genotype switch from common C/C genotype in *NOS2* in untreated cells to T/T, the SNP genotype, in talc-treated cells, except in A2780 and TOV112D (Table 2). Nevertheless, our results confirm an increase in iNOS expression and enzymatic activity in all talc-treated cells (Figure 2), again suggesting the existence of other *NOS2* SNPs. Collectively, these findings support the notion that talc treatment induced gene point mutations that happen to correspond to SNPs in locations with functional effects, thus altering overall redox balance for the initiation and development of ovarian cancer. Future studies examining such SNPs are important to fully elucidate a genotype switch mechanism induced by talc exposure.

In summary, this is the first study to clearly demonstrate that talc induces inflammation and alters the redox balance favoring a prooxidant state in normal and EOC cells. We have shown a dose-dependent significant increase in key prooxidants, iNOS, NO₂⁻/NO₃⁻, and MPO, and a concomitant decrease in key antioxidant enzymes, CAT, SOD, GPX, and GSR, in all talc-treated cells (both normal and ovarian cancer) compared to their controls. Additionally, there was a significant increase in CA-125 levels in all the talc-treated cells compared to their controls, except in macrophages. The mechanism by which talc alters the cellular redox and inflammatory balance involves the induction of specific mutations in key oxidant and antioxidant enzymes that correlate with alterations in their activities. The fact that these mutations happen to correspond to known SNPs of these enzymes indicate a genetic predisposition to developing ovarian cancer with genital talcum powder use.

Authors' Note

Ghassan M. Saed is also affiliated with Department of Gynecologic Oncology, Karmanos Cancer Institute, Detroit, MI, USA.

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Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr. Saed has served as a paid consultant and expert witness in the talcum powder litigation.

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References

1. Berek JS, Bertelsen K, du Bois A, et al. Epithelial ovarian cancer (advanced stage): consensus conference (1998) [in French]. *Gynecol Obstet Fertil*. 2000;28(7-8):576-583.

2. Jelovac D, Armstrong DK. Recent progress in the diagnosis and treatment of ovarian cancer. *CA Cancer J Clin*. 2011;61(3):183-203.
3. Prat J, Ribe A, Gallardo A. Hereditary ovarian cancer. *Hum Pathol*. 2005;36(8):861-870.
4. Ramus SJ, Vierkant RA, Johnatty SE, et al. Consortium analysis of 7 candidate SNPs for ovarian cancer. *Int J Cancer*. 2008;123(2):380-388.
5. Reuter S, Gupta SC, Chaturvedi MM, Aggarwal BB. Oxidative stress, inflammation, and cancer: how are they linked? *Free Radic Biol Med*. 2010;49(11):1603-1616.
6. Fletcher NM, Belotte J, Saed MG, et al. Specific point mutations in key redox enzymes are associated with chemoresistance in epithelial ovarian cancer. *Free Radic Biol Med*. 2016;102:122-132.
7. Cramer DW, Welch WR, Scully RE, Wojciechowski CA. Ovarian cancer and talc: a case-control study. *Cancer*. 1982;50:372-376.
8. Cramer DW, Liberman RF, Titus-Ernstoff L, et al. Genital talc exposure and risk of ovarian cancer. *Int J Cancer*. 1999;81:351-356.
9. Ness RB, Grisso JA, Cottreau C, et al. Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer. *Epidemiology*. 2000;11:111-117.
10. Henderson WJ, Joslin CA, Turnbull AC, Griffiths K. Talc and carcinoma of the ovary and cervix. *J Obstet Gynaecol Br Commonwealth*. 1971;78:266-272.
11. Terry KL, Karageorgi S, Shvetsov YB, et al. Genital powder use and risk of ovarian cancer: a pooled analysis of 8,525 cases and 9,859 controls. *Cancer Prev Res (Phila)*. 2013;6(8):811-821.
12. Penninkilampi R, Eslick GD. Perineal talc use and ovarian cancer: a systematic review and meta-analysis. *Epidemiology*. 2018;29(1):41-49.
13. Reid BM, Permuth JB, Sellers TA. Epidemiology of ovarian cancer: a review. *Cancer Biol Med*. 2017;14(1):9-32.
14. Brigelius-Flohe R, Kipp A. Glutathione peroxidases in different stages of carcinogenesis. *Biochim Biophys Acta*. 2009;1790(11):1555-1568.
15. Sun Y. Free radicals, antioxidant enzymes, and carcinogenesis. *Free Radic Biol Med*. 1990;8(6):583-599.
16. Popov B, Gadjeva V, Valkanov P, Popova S, Tolekova A. Lipid peroxidation, superoxide dismutase and catalase activities in brain tumor tissues. *Arch Physiol Biochem*. 2003;111(5):455-459.
17. Ray G, Batra S, Shukla NK, et al. Lipid peroxidation, free radical production and antioxidant status in breast cancer. *Breast Cancer Res Treat*. 2000;59(2):163-170.
18. Chung-man Ho J, Zheng S, Comhair SA, Farver C, Erzurum SC. Differential expression of manganese superoxide dismutase and catalase in lung cancer. *Cancer Res*. 2001;61(23):8578-8585.
19. Radenkovic S, Milosevic Z, Konjevic G, et al. Lactate dehydrogenase, catalase, and superoxide dismutase in tumor tissue of breast cancer patients in respect to mammographic findings. *Cell Biochem Biophys*. 2013;66(2):287-295.
20. Hu Y, Rosen DG, Zhou Y, et al. Mitochondrial manganese-superoxide dismutase expression in ovarian cancer: role in cell proliferation and response to oxidative stress. *J Biol Chem*. 2005;280(47):39485-39492.
21. Svensk AM, Soini Y, Paakko P, Hiravikoski P, Kinnula VL. Differential expression of superoxide dismutases in lung cancer. *Am J Clin Pathol*. 2004;122(3):395-404.
22. Saed GM, Ali-Fehmi R, Jiang ZL, et al. Myeloperoxidase serves as a redox switch that regulates apoptosis in epithelial ovarian cancer. *Gynecol Oncol*. 2010;116(2):276-281.
23. Galijasevic S, Saed GM, Hazen SL, Abu-Soud HM. Myeloperoxidase metabolizes thiocyanate in a reaction driven by nitric oxide. *Biochemistry*. 2006;45(4):1255-1262.
24. Galijasevic S, Maitra D, Lu T, Sliskovic I, Abdulhamid I, Abu-Soud HM. Myeloperoxidase interaction with peroxynitrite: chloride deficiency and heme depletion. *Free Radic Biol Med*. 2009;47(4):431-439.
25. Fletcher NM, Jiang Z, Ali-Fehmi R, et al. Myeloperoxidase and free iron levels: potential biomarkers for early detection and prognosis of ovarian cancer. *Cancer Biomark*. 2011;10(6):267-275.
26. Scholler N, Urban N. CA125 in ovarian cancer. *Biomark Med*. 2007;1(4):513-523.
27. Belotte J, Fletcher NM, Saed MG, et al. A single nucleotide polymorphism in catalase is strongly associated with ovarian cancer survival. *PLoS One*. 2015;10(8):e0135739.

Exhibit 37

New Insights into the Pathogenesis of Ovarian Cancer: Oxidative Stress

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Additional information is available at the end of the chapter

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Abstract

Ovarian cancer is the leading cause of death from gynecologic malignancies yet the underlying pathophysiology is not clearly established. Epithelial ovarian cancer (EOC) has long been considered a heterogeneous disease with respect to histopathology, molecular biology, and clinical outcome. Treatment of ovarian cancer includes a combination of cytoreductive surgery and combination chemotherapy, with platinum and taxanes. Despite initial success, over 75% of patients with advanced disease will relapse around 18 months and the overall 5-year survival is approximately 50%. Cancer cells are known to be under intrinsic oxidative stress, which alters their metabolic activity and reduces apoptosis. Epithelial ovarian cancer has been shown to manifest a persistent pro-oxidant state as evident by the upregulation of several key oxidant enzymes in EOC tissues and cells. In the light of our scientific research and the most recent experimental and clinical observations, this chapter provides the reader with up to date most relevant findings on the role of oxidative stress in the pathogenesis and prognosis of ovarian cancer, as well as a novel mechanism of apoptosis/survival in EOC cells.

Keywords: ovarian cancer, oxidative stress, chemoresistance, apoptosis, nitrosylation, caspase-3

1. Introduction

Ovarian cancer is the fifth leading cause of cancer death; the leading cause of death from gynecologic malignancies, and the second most commonly diagnosed gynecologic malignancy; yet the underlying pathophysiology continues to be delineated [1, 2]. Epithelial ovarian cancer

has long been considered a heterogeneous disease with respect to histopathology, molecular biology, and clinical outcome. It comprises at least five distinct histological subtypes, the most common and well-studied being high-grade serous ovarian cancer (HGSOC) [3]. The majority of advanced-stage tumors are of epithelial cell origin and can arise from serous, mucinous, or endometrioid cells on the surface epithelium of the ovary or the fallopian tube [2]. The most obvious clinical implication of tumor heterogeneity is that molecular-targeted therapy, while being effective at one tumor site, may not be as effective at all of them [3].

Because early-stage ovarian cancer presents with nonspecific symptoms, most often diagnosis is not made until after the malignancy has spread beyond the ovaries [4]. Mortality rates for this type of malignancy are high because of a lack of a sensitive and specific early-stage screening method [4]. Surgical cytoreduction followed by platinum/taxane chemotherapy results in complete clinical response in 50–80% of patients with stage III and IV disease, but most will relapse within 18 months and ultimately develop chemoresistant disease [2]. Resistance to chemotherapy can either be intrinsic, occurring at the onset of treatment, or acquired, when the disease recurs despite an initially successful response [5–7]. Attempts to overcome drug resistance are central to both clinical and basic molecular research in cancer chemotherapy [5, 8]. Cancer cells are known to be under intrinsic oxidative stress, resulting in increased DNA mutations or damage, genome instability, and cellular proliferation [9–13]. The persistent generation of cellular reactive oxygen species (ROS) is a consequence of many factors including exposure to carcinogens, infection, inflammation, environmental toxicants, nutrients, and mitochondrial respiration [14–17].

The origin and causes of ovarian tumors remains under debate. Injury to surface epithelial ovarian cells due to repeated ovulation is thought to induce tumorigenesis in these cells and is known as the “incessant ovulation hypothesis.” Additionally, hormonal stimulation of the surface epithelium of the ovary has been described to initiate tumorigenesis in surface epithelial cells and is known as the “gonadotropin hypothesis.” Moreover, the fallopian tube, and not the ovary, has been suggested to be the origin for most epithelial ovarian cancer [2, 18, 19]. Nevertheless, many cases of ovarian cancer continue to be described as *de novo*.

Histopathologic, clinical and molecular genetic profiles were successfully utilized to clearly discriminate between type I and type II ovarian tumors [19]. Accordingly, type I ovarian tumors develop from benign precursor lesions that implant on the ovary and include clear cell, endometrioid, low-grade serous carcinomas, mucinous carcinomas and malignant Brenner tumors [19]. Type II ovarian tumors develop from intraepithelial carcinomas of the fallopian tube and can then spread to involve both the ovary as well as other sites, such as high-grade serous carcinomas which comprise morphologic and molecular subtypes [19]. Additionally, high-grade endometrioid, poorly differentiated ovarian cancers, and carcinosarcomas are also classified as type II tumors.

Attempts to identify specific genes in ovarian tumors to help in early detection of the disease and serve as targets for improved therapy had failed to identify reproducible prognostic indicators [2, 20–22]. Several oncogenic mutations and pathways have been identified in ovarian cancer. Specific inherited mutations in the *BRCA1* and *BRCA2* genes that produce tumor suppressor proteins, are known to be associated with a 15% increased risk of ovarian cancer overall [2]. Ovarian cancers associated with *BRCA1* and *BRCA2* mutations are much more common in

younger age patients as compared with their nonhereditary counterparts. Additionally, somatic gene mutations in RAD51C and D, HNPCC, NF1, RB1, CDK12, P53, BRAF, KRAS, PIK3CA, and PTEN have been identified in epithelial ovarian cancer. Somatic mutations in BRAF and KRAS genes are relatively common in type I tumors, while p53 mutations, RAS signaling and PIK3CA are common in type II. Additional genetic variations have been hypothesized to act as low to moderate alleles, which contribute to ovarian cancer risk, as well as other diseases [23].

Ovarian tumors are distinct from many other type of cancers as they rarely metastasize outside of the peritoneal cavity [24]. Ovarian tumors are spread into the peritoneal cavity when cells from the primary tumor detach and travel into the peritoneum where they implant into the mesothelial lining [25]. Metastases beyond the peritoneum are usually restricted to recurrent or advanced disease; however, pleural metastases were reported to be present at initial diagnosis. Moreover, the recent discovery of ovarian cancer stem cells, which manifest properties of typical cancer stem cells, in ascites is a new additional contributing factor to not only to metastasis but also to chemoresistance [25, 26].

2. Oxidative stress

Homeostasis, the balance between the production and elimination of oxidants, is maintained by mechanisms involving oxidants and antioxidant enzymes and molecules. If this balance is altered, it leads to an enhanced state of oxidative stress that alters key biomolecules and cells of living organism [13]. Oxidant molecules are divided into two main groups; oxygen-derived or nitrogen-containing molecules. Oxygen-derived molecules, also known as reactive oxygen species (ROS), includes free radicals such as hydroxyl (HO^\bullet), superoxide ($\text{O}_2^{\bullet-}$), peroxy (RO_2^\bullet), and alkoxyl (RO^\bullet), as well as oxidizing agents such as hydrogen peroxide (H_2O_2), hypochlorous acid (HOCl), ozone (O_3), and singlet oxygen ($^1\text{O}_2$) that can be converted to radicals [13, 27]. Nitrogen containing oxidants, also known as reactive nitrogen species (RNS), are derived from nitric oxide (NO) that is produced in the mitochondria in response to hypoxia [13]. Exposure to inflammation, infection, carcinogens, and toxicants are major sources of ROS and RNS, *in vivo* [13, 16, 27, 28]. Additionally, RNS and ROS can be produced by various enzymes including cytochrome P450, lipoxygenase, cyclooxygenase, nicotinamide adenine dinucleotide phosphate (NAD(P)H) oxidase complex, xanthine oxidase (XO), and peroxisomes (**Figure 1**) [13, 28, 29].

To maintain the redox balance, ROS and RNS are neutralized by various important enzyme systems including superoxide dismutase (SOD), catalase (CAT), glutathione S-transferase (GST), glutathione (GSH), thioredoxin coupled with thioredoxin reductase, glutaredoxin, glutathione peroxidase (GPX), and glutathione reductase (GSR) (**Figure 1**) [27]. Superoxide dismutase is known to convert $\text{O}_2^{\bullet-}$ to H_2O_2 , which is then converted to water by CAT. Glutathione S-transferase is involved in detoxification of carcinogens and xenobiotics by catalyzing their conjugation to GSH that will aid in expulsion from the cell (**Figure 1**) [27]. Indeed, the GSH-to-oxidized-GSH (GSH/GSSG) ratio is a good indicator of cellular redox buffering capacity [30, 31]. Under enhanced oxidative stress, the GSH/GSSG complex is known to stimulate the activity of the GS-X-MRP1 efflux pump, which removes toxins from cells. This mechanism has been investigated in the development of resistance to chemotherapeutic drugs [30, 31].

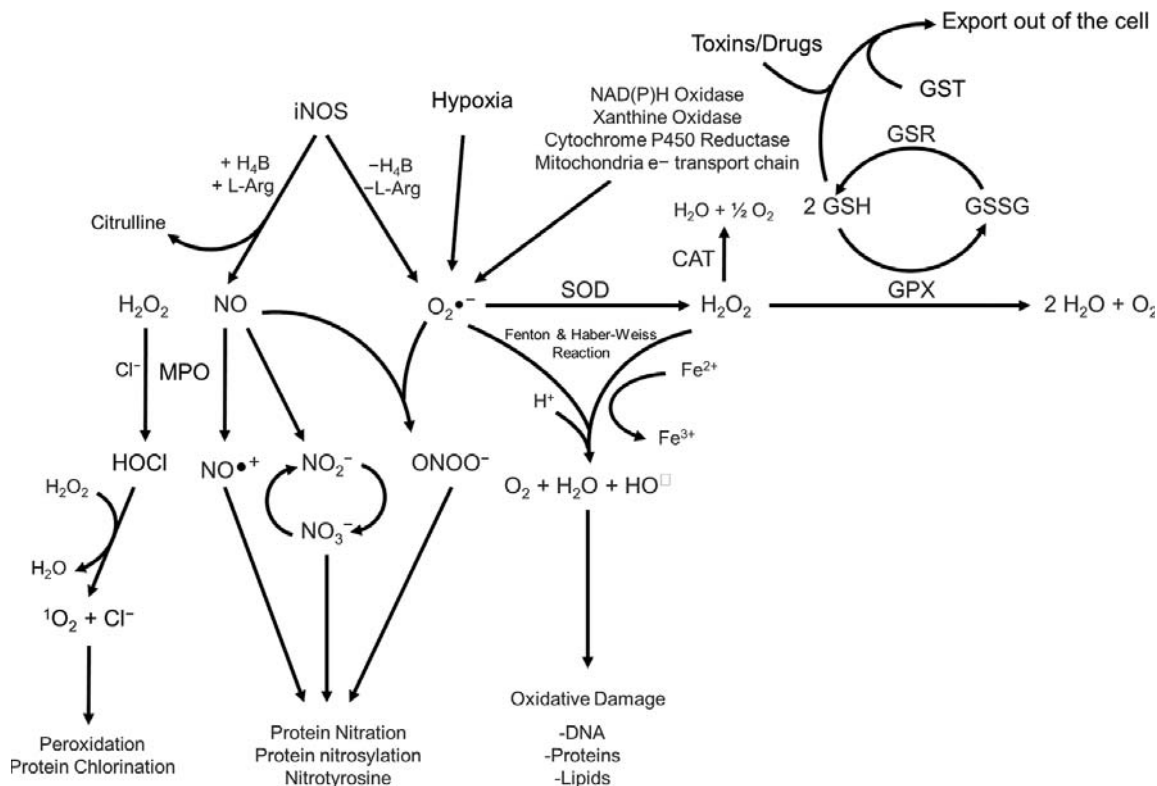


Figure 1. Summary of key oxidant and antioxidants in cancer [1]. Abbreviations are CAT, catalase; Cl^- , chloride ion; Fe_2^+ , iron (II); Fe_3^+ , iron (III); GPX, glutathione peroxidase; GSH, glutathione; GSR, glutathione reductase; GSSG, reduced glutathione; GST, glutathione S-transferase; H_2O_2 , hydrogen peroxide; H_4B , tetrahydrobiopterin; HO^\bullet , hydroxyl radical; HOCl, hypochlorous acid; iNOS, inducible nitric oxide synthase; L-Arg, L-arginine; MPO, myeloperoxidase; NAD(P)H, nicotinamide adenine dinucleotide phosphate; $\text{NO}^\bullet+$, nitrosonium cation; NO_2^- , nitrite; NO_3^- , nitrate; $\text{O}_2^{\bullet-}$, superoxide; ONOO $^-$, peroxynitrite; SOD, superoxide dismutase.

3. Oxidative stress and cancer

Oxidative stress has been implicated in the etiology of several diseases, including cancer. Alteration of the cellular redox balance modulates the initiation, promotion, and progression of tumor cells [13, 27]. The continuous generation of oxidants and free radicals affects key cellular mechanisms that control the balance of cell proliferation and apoptosis, which play a major role in the initiation and development of several cancers. Depending on the concentration of ROS and RNS in the cellular environment, oxidants can initiate and promote the oncogenic phenotype or induce apoptosis, and thus act as antitumor agents [32]. Several transcription factors that modulate the expression of genes critical to the development and metastasis of cancer cells are known to be controlled by oxidative stress. This includes hypoxia inducible factor (HIF)-1 α , nuclear factor (NF)- κ B, peroxisome proliferator-activated receptor (PPAR)- γ , activator protein (AP)-1, β -catenin/Wnt, and Nuclear factor erythroid 2-related factor 2 (Nrf2) [13]. The transcription factor regulator Nrf2 is known to control the expression of some key antioxidant enzymes that are needed to scavenge oxidants and free radicals [13, 33]. The activation of Nrf2 involves the suppressor protein, Kelch-like ECH-associated protein 1

(Keap1), that binds Nrf2 in the cytoplasm and prevents its translocation into the nucleus, where it binds to promoters of antioxidant enzymes [13, 33]. Additionally, oxidative stress is known to activate certain signaling pathways, specifically, the MAPK/AP-1 and NF- κ B pathways, which are critical for the initiation and maintenance of the oncogenic phenotype [34].

More importantly, ROS and RNS are known to induce genetic mutations that alter gene expression as well as induce DNA damage, and thus have been implicated in the etiology of several diseases, including cancer [2, 13, 35]. Damage to DNA by ROS and RNS is now accepted as a major cause of cancer, and has been demonstrated in the initiation and progression of several cancers including breast, hepatocellular carcinoma, and prostate cancer [34]. Oxidative stress is known to modify all the four DNA bases by base pair substitutions rather than base deletions and insertions. Modification of GC base pairs usually results in mutations, whereas, modification of AT base pairs does not [36]. Modification of guanine in cellular DNA, causing G to T transversions, is commonly induced by ROS and RNS [34]. If not repaired, the transversion of G to T in the DNA of oncogenes or tumor suppressor genes can lead to initiation and progression of cancer. Oxidation of DNA bases, such as thymidine glycol, 5-hydroxymethyl-2'-deoxyuridine, and 8-OHdG are now accepted markers of cellular DNA damage by free radicals [35].

Oxidants and free radicals are known to enhance cell migration contributing to the enhancement of tumor invasion and metastasis, main causes of death in cancer patients [2, 13]. Reactive oxygen species, through the activation of NF- κ B, regulate the expression of intercellular adhesion protein-1 (ICAM-1), a cell surface protein in various cell types [13]. In response to oxidative stress, the interleukin 8 (IL-8)-induced enhanced expression of ICAM-1 on neutrophils enhances the migration of neutrophils across the endothelium, which is key in tumor metastasis [13]. Another important player that controls cell migration and consequently, tumor invasion, is the upregulation of specific matrix metalloproteinases (MMPs), essential enzymes in the degradation of most components of the basement membrane and extracellular matrix, such as type IV collagen [13, 37]. The expression of MMPs, such as MMP-2, MMP-3, MMP-9, MMP-10, and MMP-13 is enhanced by free radicals, specifically H₂O₂ and NO, through the activation of Ras, ERK1/2, p38, and JNK, or the inactivation of phosphatases [13, 37]. Indeed, the major source of cellular ROS, the NAD(P)H oxidase family of enzymes, has been linked to the promotion of survival and growth of tumor cells in pancreatic and lung cancers [2, 13].

Oxidants and free radicals are also known to enhance angiogenesis, a key process for the survival of solid tumors [13]. Angiogenesis involves the upregulation of vascular endothelial growth factor (VEGF) or the downregulation of thrombospondin-1 (TSP-1), an angiogenesis suppressor in response to oxidative stress [13]. This process is controlled by several oncogenes and tumor-suppressor genes such as Ras, c-Myc, c-Jun, mutated p53, human epidermal growth factor receptor-2, and steroid receptor coactivators [38, 39]. Additionally, oxidants and free radicals are known to stabilize HIF-1 α protein and induce the production of angiogenic factors by tumor cells.

4. Cancer cells are under intrinsic oxidative stress

Cancer cells are continuously exposed to high levels of intrinsic oxidative stress due to increased aerobic glycolysis (Warburg effect), a known process in cancer cell metabolism [10, 40].

Thus, cancer cells trigger several critical adaptations that are essential for their survival such as suppression of apoptosis, alteration of glucose metabolism, and stimulation of angiogenesis [10, 29]. Oxygen depletion, due to a hypoxic microenvironment, significantly stimulates mitochondria to produce high levels of ROS and RNS which is known to activate HIF-1 α and consequently promote cell survival in such an environment [29]. The half-life of HIF-1 α is extremely short as it is rapidly inactivated through hydroxylation reactions mediated by dioxygen, oxaloglutarate, and iron-dependent prolyl 4-hydroxylases, located in the nucleus and cytoplasm [40, 41]. Nitric oxide and other ROS, as well as H₂O₂ efflux into the cytosol due to dismutation of O₂^{•-}, can inhibit prolyl 4-hydroxylases activity, leading to the stabilization of HIF-1 α [29, 42]. More importantly, stabilization of HIF-1 α , under hypoxic conditions, can be blocked when inhibiting ROS production in mitochondria that lack cytochrome c [29, 43].

Pro-oxidant enzymes such as myeloperoxidase (MPO), inducible nitric oxide synthase (iNOS) and NAD(P)H oxidase have been associated with initiation, progression, survival, and increased risk in cancers such as breast, ovarian, lung, prostate, bladder, colorectal and malignant melanoma [21, 44]. Moreover, the expression of those key pro-oxidant enzymes was found to change based on the histological type and grade of the tumor [21, 45, 46]. Likewise, antioxidants have also been associated with initiation, progression, survival, and increased risk in cancers such as lung, head and neck, and prostate cancer [47–50]. The expression of GSR and GPX, key antioxidant enzymes, has also been reported to be altered in various types of cancer [21]. The activity and expression of SOD, a powerful antioxidant enzyme, has been reported to be decreased in colorectal carcinomas, pancreatic, lung, gastric, ovarian, and breast cancers [21, 45, 46]. Likewise, the expression and activity of CAT, a key antioxidant enzyme, was reported to be decreased in breast, bladder, and lung cancers but increased in brain cancer [21, 45, 46]. Antioxidant enzymes play a critical role in maintaining the redox balance in the presence of microenvironment stress, and thus, alteration of this balance may provide a unique and complex microenvironment for cancer cell survival.

5. Ovarian cancer cells manifest a persistent pro-oxidant state

Recent evidence suggests that oxidative stress is a critical factor in the initiation and development of several cancers, including ovarian cancer [40, 51]. Consistently, it has been reported that ovarian cancer patients manifested significantly decreased levels of antioxidants and higher levels of oxidants [10, 22, 40, 51–53]. An enhanced redox state, resulting from increased expression of key pro-oxidant enzymes and decreased expression of antioxidant enzymes, has been extensively described in epithelial ovarian cancer (EOC) [52–54]. We have previously reported that MPO, a hemoprotein present solely in myeloid cells that acts as a powerful oxidant, and iNOS, a key pro-oxidant enzyme, are highly expressed and co-localized to the same cell in EOC cells [53]. These two enzymes, MPO and iNOS, work together to inhibit apoptosis, a hallmark of ovarian cancer cells. Nitric oxide, produced by iNOS, is used by MPO as a one-electron substrate to generate nitrosonium cation (NO⁺), a labile nitrosating species, resulting in a significant increase in S-nitrosylation of caspase-3, which inhibits apoptosis [53, 55, 56]. Indeed, attenuating oxidative stress by inhibiting MPO or iNOS significantly induced

apoptosis in EOC cells [54]. Moreover, the remarkably higher levels of iNOS/NO, produced by EOC cells, resulted in the generation of high levels of nitrate and nitrite, powerful protein nitration agents that are known to stimulate the initiation and progression of tumor cells [53]. Under oxidative stress, where both NO and $O_2^{\bullet-}$ are elevated, MPO was reported to serve as a source of free iron which reacts with H_2O_2 and generated highly reactive hydroxyl radical (HO^{\bullet}), further increasing oxidative stress [22, 53]. Additionally, EOC cells are also characterized by enhanced expression of NAD(P)H oxidase, a potent oxidant enzyme that is known to be the major source of $O_2^{\bullet-}$ in the cell. Such high levels of $O_2^{\bullet-}$ combined with significantly high levels of NO generates peroxynitrite, another powerful nitrosylation and nitration agent, which modifies proteins and DNA structure and function in cells [57].

Recently we have gathered compelling evidence demonstrating that talc, through alteration of the redox balance, can generate a similar pro-oxidant state in both normal ovarian epithelial and ovarian cancer cells. Talc and asbestos are both silicate minerals, and the carcinogenic effects of asbestos have been extensively studied and documented in the medical literature [58]. Asbestos fibers in the lung initiate an inflammatory and scarring process, and it has been proposed that ground talc, as a foreign body, might initiate a similar inflammatory response [58]. Although there is strong epidemiological evidence to suggest an association between talc use and ovarian cancer, the direct link and precise mechanisms have yet to be elucidated. We investigated the effect of talc on both oxidants and antioxidants in normal ovarian epithelial and ovarian cancer cell lines. There was a marked increase in mRNA levels of the pro-oxidant enzymes, iNOS and MPO in talc treated ovarian cancer cell lines and normal ovarian epithelial cells, all as compared to their control, as early as 24 hours. Additionally, there was a marked decrease in the mRNA levels of the antioxidant enzymes CAT, GPX, SOD3, but with a marked increase in GSR, and no change in GST, in talc treated ovarian cancer cell line and in normal ovarian epithelial cells, all compared to their control, as early as 24 hours (*data not published*). Thus, there is a direct effect of talc on the molecular levels of oxidant and antioxidants, elucidating a potential mechanism for the development of ovarian cancer in response to talc.

6. Biomarkers for the early detection of ovarian cancer

The discovery of MPO expression in ovarian EOC cells and tissues was surprising, as it is only expressed by cells of myeloid origin. Intriguingly, the combination of serum MPO and free iron was reported to potentially serve as biomarkers for early detection of ovarian cancer [22]. A robust detection method based on molecular profiles for ovarian cancer has not yet been developed because the disease exhibits a wide range of morphological, clinical and genetic variations during its progression. The search for non-invasive, cost-effective ovarian cancer biomarker tests has been ongoing for many years. Immunizations of mice with ovarian cancer cells has led to hybridoma validation by ELISA, while flow cytometry analysis permitted the discovery of cancer antigen (CA)-125 and mesothelin [59]. Furthermore, the screening of an array of 21,500 unknown ovarian cDNAs hybridized with labeled first-strand cDNA from ten ovarian tumors and six normal tissues led to the discovery of human epididymis protein 4 (HE4) [60]. Most interestingly, HE4 is overexpressed in 93% of serous and 100% of endometrioid

EOCs, and in 50% of clear cell carcinomas, but not in mucinous ovarian carcinomas [61]. Thus, HE4 was identified as one of the most useful biomarkers for ovarian cancer, although it lacked tissue-specificity [60, 62–64]. Secreted HE4 high levels were also detected in the serum of ovarian cancer patients [65]. Additionally, combining CA-125 and HE4 is a more accurate predictor of malignancy than either alone [66–68].

Multi-marker panels have the potential for high positive predictive values (PPVs), but careful validation with appropriate sample cohorts is mandatory and complex algorithms may be difficult to implement for routine clinical use [59]. Panels of biomarkers have been extensively investigated to improve sensitivity and specificity and have included some of the most promising reported markers such as CA72-4, M-CSF, OVX1, LPA, prostacin, osteopontin, inhibin and kallikrein [69–71]. However, most of these tests frequently require certain equipments and complex computational algorithms that may not be available in a standard immunoassay laboratory, [32]. Among postmenopausal women in the U.S., only 1 in 2500 women are reported with ovarian cancer. Due to this low prevalence of the disease, a screening method that yield a 75% sensitivity and 99.6% specificity to achieve a PPV value of 10% to be effective for the detection of all stages of ovarian cancer [72]. To date, there is no single biomarker available that met these requirements.

The established role of MPO in oxidative stress and inflammation has been a leading factor in the study of MPO as a possible marker of plaque instability and a useful clinical tool in the evaluation of patients with coronary heart disease [73]. Recent genetic studies implicated MPO in the development of lung cancer by demonstrating a striking correlation between the relative risk for development of the disease and the incidence of functionally distinct MPO polymorphisms [74]. Myeloperoxidase levels reported for various inflammatory disorders are coincidentally lower than those levels found in all stages of ovarian cancer. A previous study reported normal serum MPO and iron levels as 62 ± 11 ng/ml and 96 ± 9 μ g/dl, respectively [75]. However, there was a significant increase in serum MPO and iron levels to 95 ± 20 ng/ml and 159 ± 20 μ g/dl, respectively, in asthmatic individuals [75]. Although there was an increase in this reported serum iron, these levels still fell within the normal range (50 to 170 μ g/dl) [22, 75]. Other studies have showed that an elevated MPO levels, reaching up to 350 ng/ml, in serum plasma, was indicative of a higher risk for cardiovascular events in patients hospitalized for chest pain [76, 77]. A recent study showed a significant correlation between MPO levels and the stage of ovarian cancer, as is the linear trend for MPO with increasing stage [22]. Similarly, there was a significant difference in the level of free iron in serum and tissues obtained from stage I as compared to combined stages II, III, and IV ovarian cancer. There was an overlap between stage I ovarian cancer and inflammation (endometriosis) serum MPO levels, however serum free iron levels were significantly higher in stage I ovarian cancer as compared to inflammation. There was no significant change in free iron levels between the healthy control group, benign gynecologic conditions group, and inflammation group [22].

Due to the overlap of MPO levels in early-stage ovarian cancer and inflammatory conditions, there is a potential for a false positive with MPO alone in patients with cardiovascular, inflammation, and/or asthmatic disorders. It has been reported that MPO heme destruction and iron release is mediated by high levels of both HOCl (a product of MPO) and oxidative stress (i.e. cancer) [22]. The free iron generated by hemoprotein destruction not only contributes to elevation of

serum iron levels, but may also induce oxidative stress, which can promote lipid peroxidation, DNA strand breaks, and modification or degradation of biomolecules [78–80]. Iron reacts with H_2O_2 and catalyzes the generation of highly reactive hydroxyl radicals, which in turn further increases free iron concentrations by the Fenton and Haber–Weiss reaction [81]. Several studies from our laboratories have provided a mechanistic link between oxidative stress, MPO, higher levels of HOCl and higher free iron that could explain the observed accumulation of free iron in epithelial ovarian cancers tissues [53, 82–85]. Utilizing serum iron levels alone as a biomarker is also not sufficient for early detection of ovarian cancer due to many uncontrolled variables, i.e. dietary intake, supplements, effects of other iron-generating enzymes or factors, and more importantly they are not as specific as MPO levels. Specifically, in iron deficiency anemic patients, their free iron levels may become a confounding factor in its utilization for early detection of ovarian cancer. Thus, anemia should be ruled out to eliminate any overlap that would lead to misdiagnosis. The incorporation of iron deficiency anemic patients in a logistic regression model will help determine its overlap with early-stage ovarian cancer. Additionally, currently available clinical studies focused on either biochemical or more recently, genetic markers of iron overload have reported conflicting results regarding the use of iron levels alone for diagnosis [86–89].

Thus, the combination of serum MPO and iron levels should yield a higher power of specificity and sensitivity that should distinguish women with early-stage ovarian cancer from other disorders, specifically inflammation [22]. Additionally, combining serum MPO and iron levels with the best currently existing biomarkers through the creation of a logistic regression model may increase the overall predictive values. Collectively, there is a role for serum MPO and free iron in the pathophysiology of ovarian cancer, which thereby qualifies them to serve as biomarkers for early detection and prognosis of ovarian cancer.

7. Modulation of oxidative stress

Several studies have reported the beneficial effects of modulating the redox status of cancer cells, however few studies have been reported for ovarian cancer [90–92]. Inhibition of pro-oxidant enzymes, such as NAD(P)H oxidase, has been shown to significantly induce apoptosis of cancer cells [93, 94]. We investigated whether NAD(P)H oxidase-mediated generation of intracellular reactive ROS lead to anti-apoptotic activity and thus a growth advantage to EOC cells. Diphenyleneiodonium (DPI) has been used to inhibit ROS production mediated by NAD(P)H oxidase in various cell types [95–97]. Our results showed that NAD(P)H oxidase is over-expressed in EOC tissues and cells as compared to normal ovarian tissues and cells [52]. Indeed, high levels of NAD(P)H oxidase are known to promote tumorigenesis of NIH3T3 mouse fibroblasts and the DU-145 prostate epithelial cells [98].

Inhibition of NAD(P)H oxidase has also been reported to decrease the generation of $\text{O}_2^{\bullet-}$, H_2O_2 , as well as other oxidants [93, 94]. Cancer cells are known to manifest enhanced intrinsic oxidative stress and metabolic activity that lead to mitochondrial failure [99, 100]. Indeed, it was previously reported that ovarian tumors are characterized by increased ROS levels as evident from increased $\text{O}_2^{\bullet-}$ generated from NAD(P)H oxidase as well as mitochondrial malfunction [101]. The NAD(P)H oxidase redox signaling is controlled by mitochondria, and thus loss of

this control is thought to contribute to tumorigenesis [101]. Others have also shown that inhibition of NAD(P)H oxidase induced apoptosis in cancer cells [102]. Continuous ROS production by the cell and the environment further induces the inhibition of phosphorylation of AKT and subsequent suppression of AKT-mediated phosphorylation of ASK1 on Ser-83, resulting in significant decrease in apoptosis [102–104]. Furthermore, paclitaxel, a chemotherapeutic agent used in the treatment of ovarian cancer and other cancers, induced apoptosis of ovarian cancer cells by negative regulation of AKT–ASK1 phosphorylation signaling [102–104]. On the other hand, activation of AKT by ROS provided protection against apoptosis [102–104].

Data from our laboratory clearly demonstrated that treatment of EOC cells with DPI, which inhibits ROS production mediated by NAD(P)H oxidase, significantly reduced SOD3 and HIF-1 α mRNA and protein levels as early as 30 minutes after treatment with a concomitant increase in apoptosis [52]. The association between increased HIF-1 α expression and decreased cellular apoptosis has also been demonstrated in lung and hepatoma cancer cells [94, 105]. Overexpression of HIF-1 α is thought to decrease apoptosis by the upregulation of anti-apoptotic proteins, Bcl-2 and Bcl-xL and down regulation of pro-apoptotic proteins, BAX and BAK [106]. Inhibition of HIF-1 α by rapamycin increased apoptosis by decreasing the expression of apoptosis inhibitor Bcl-2 in ovarian cancer xenografts [107]. Additionally, inhibition of HIF-1 α by rapamycin enhanced apoptosis through the inhibition of cell survival signals in several other cell lines [107].

Most of the NAD(P)H oxidase-generated $O_2^{\bullet-}$ is utilized to produce H_2O_2 by nonenzymatic or SOD-catalyzed reactions [108–110]. Hydrogen peroxide serves as the precursor of more toxic hydroxyl radicals and thus is extremely destructive to cells and tissues [109–111]. The expression of SOD3 was reported to increase in response to intrinsic oxidative stress in ovarian cancer cells [112]. It has been demonstrated that overexpression of the SOD3 gene significantly suppressed lung cancer metastasis as well as inhibited the growth of B16-F1 melanoma tumors in mice [113, 114]. However, in a somewhat controversial study, it has been shown that inhibition of SOD selectively induced apoptosis of leukemia and ovarian cancer cells [10].

Under hypoxic conditions, SOD3 is overexpressed and has been reported to significantly induce the expression of HIF-1 α in tumors through unknown mechanisms however, steady state levels of $O_2^{\bullet-}$ and the stabilization of HIF-1 α have been proposed to play a role in this mechanism [107, 115]. Therefore, inhibition of NAD(P)H oxidase and the consequent reduction of $O_2^{\bullet-}$ levels may destabilize HIF-1 α , and subsequently increase apoptosis by lowering SOD3 levels. Thus, we conclude that lowering oxidative stress, possibly through the inhibition of NAD(P)H oxidase-generated $O_2^{\bullet-}$, induces apoptosis in ovarian cancer cells and may serve as a potential target for cancer therapy. This effect was attributed to the modulation of key enzymes that are central to controlling the cellular redox balance.

8. Modulation of metabolism

Cancer cells are known to favor anaerobic metabolism, even when oxygen is present and is known as the “Warburg effect” [116, 117]. Aerobic glycolysis is known to decrease ATP yield as well as increase lactate production by cancer cells [116–118]. To compensate for this decrease in

ATP, cancer cells significantly increase glucose uptake through upregulation of glucose receptors [40, 41, 118]. Increased lactate in cancer cells enhances lactic acidosis, which is significantly toxic to the surrounding tissues and can facilitate tumor growth through the stimulation of ECM degradation, angiogenesis, and metastasis [118]. Additionally, aerobic glycolysis in cancer cells activates HIF, an oxygen-sensitive transcription factor that plays an important role in initiation and maintenance of the oncogenic phenotype [118]. In this regard, HIF induces the expression of several glucose transporters and glycolysis enzymes as well as induces the expression of pyruvate dehydrogenate kinase (PDK), an enzyme that stimulates pyruvate entry into the mitochondria for oxidation [41, 118, 119]. Thus, shifting glucose metabolism in cancer cells from glycolysis to glucose oxidation may have therapeutic value [120]. Indeed, inhibiting PDK by dichloroacetate (DCA) has been reported to induce apoptosis in tumor cells and significantly decreased HIF-1 α expression [40]. More importantly DCA is currently in the clinical use for the treatment of hereditary mitochondrial diseases as well as lactic acidosis [41, 121]. The use of DCA at a dose of 35 to 50 mg/kg decreased lactate levels by more than 60% [41, 122]. Dichloroacetate treatment has been shown to significantly induce apoptosis, through the stimulation of caspase-3 activity, in a dose-dependent manner in EOC cells as well as other cancers, such as glioblastoma, endometrial, prostate, and non-small cell lung cancers [40, 123]. Aerobic glycolysis is associated with resistance to apoptosis in cancer cells as many of the enzymes in the glycolysis process are known to modulate gene transcription of apoptotic proteins [40, 41, 69, 124]. Stimulation of pyruvate entry into the mitochondria by DCA, through activation of PDH and inhibition of PDK, is an ideal method to shift aerobic glycolysis to glucose oxidation as inhibiting aerobic glycolysis results in ATP depletion and necrosis, not apoptosis [41, 125].

An additional approach to induce apoptosis in cancer cells is through scavenging high levels of oxidants produced by cancer cells utilizing antioxidants [126]. Deficiency in SOD or inhibition of SOD enzyme activity causes accumulation of O₂^{•-} which is the precursor for several toxic free radicals that are critical to the oncogenic process [127]. Elevated levels of oxidants and free radicals are also known to induce cellular senescence and necrosis, and thus can kill tumor cells [40, 128]. The precise effect of high levels of oxidants and free radicals in cancer cells will depend on the type of cells and tissues, the site of production, and the type and concentration of oxidants [13].

9. Chemotherapy and the acquisition of chemoresistance in EOC cells

Resistance to taxanes and platinum, chemotherapy drugs in current use for ovarian cancer treatment, remains a major obstacle to a successful treatment of ovarian cancer patients [6]. Resistance to chemotherapy not only limits the use of the initial drug but also limits the use of other agents, even those with different mechanisms of action [129]. Chemotherapy drugs exert their actions by the initiation of cell death either directly through the generation of oxidative stress or as an indirect effect of exposure, as observed with several chemotherapeutic agents [130]. The development of chemoresistance to drugs is dependent on several factors that include: influx/efflux of drugs that decrease platinum accumulation in tumor cells, enhanced GSH and GST levels, upregulation of anti-apoptotic proteins such as Bcl-2, loss of tumor necrosis factor receptor ligand which induces apoptosis, increased DNA repair through up-regulation of repair

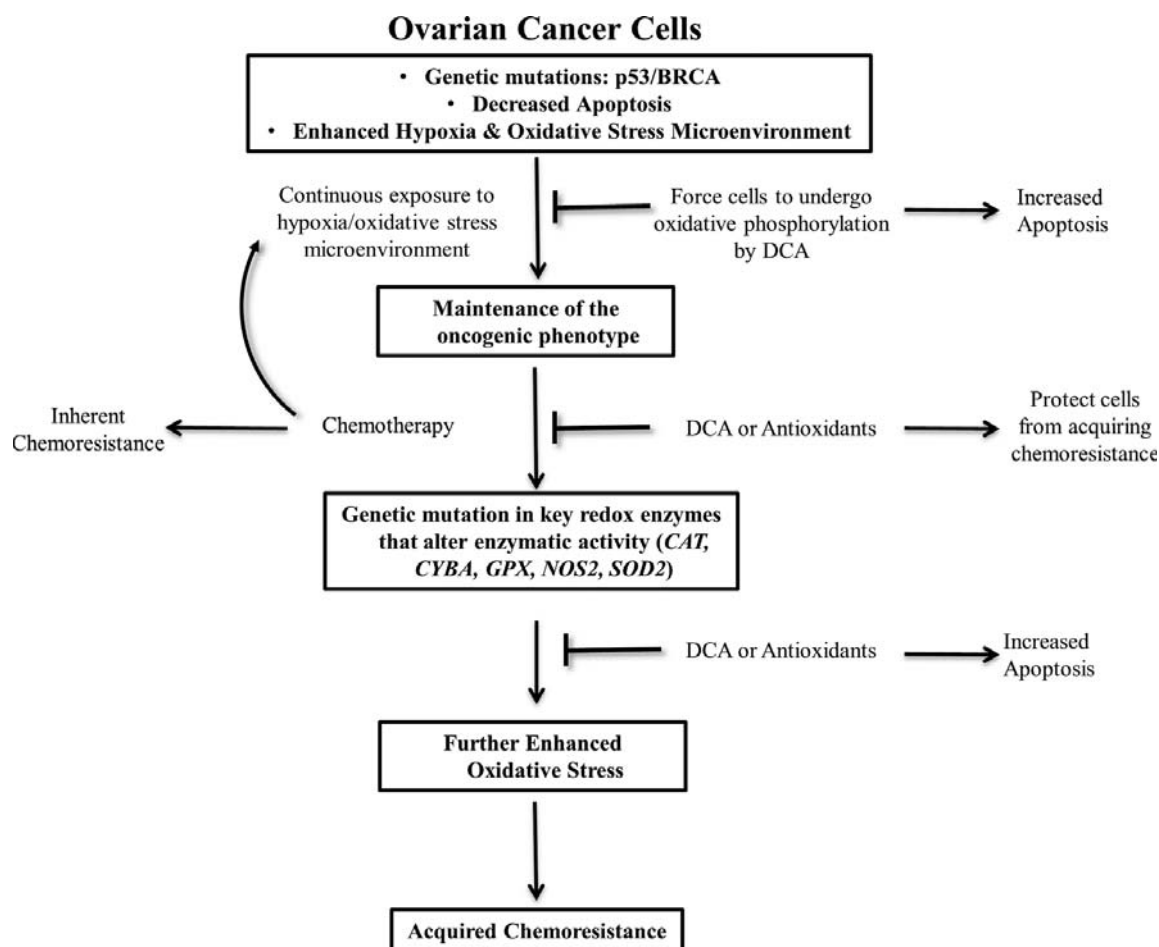


Figure 2. Summary of the role of oxidative stress in the development of sensitive and chemoresistant ovarian cancer [1].

genes, and loss of functional p53 that augments NF- κ B activation [13, 131]. We have previously shown that chemoresistant EOC cells manifested increased iNOS and nitrate/nitrite levels as well as a decrease in GSR expression as compared to sensitive EOC cells, suggesting a further enhancement of the redox state in chemoresistant cells [1, 45]. Additionally, CAT, GPX, and iNOS were shown to be significantly increased while, GSR, SOD, and the NAD(P)H oxidase subunit (p22^{phox}) were decreased in chemoresistant EOC cells as compared to their sensitive counterparts [21]. These finding supports a key role for oxidative stress, not only in the development of the oncogenic phenotype, but also in the development of chemoresistance (**Figure 2**).

10. Common polymorphisms in redox enzymes are associated with ovarian cancer

A single nucleotide polymorphism (SNP) occurs as a result of gene point mutations with an estimated frequency of at least one in every 1000 base pairs that are selectively maintained and distributed in populations throughout the human genome [132]. An association

between common SNPs in oxidative DNA repair genes and redox genes with human cancer susceptibility has been established [28]. Common SNPs in the redox enzymes are known to be strongly associated with an altered enzymatic activity in these enzymes, and may explain the enhanced redox state that has been linked to several malignancies, including ovarian cancer [40, 52]. Additionally, it may further explain the observation of significantly decreased apoptosis and increased survival of EOC cells [53]. It is therefore critical to determine the exact effect of common SNPs in various redox enzymes on all process involved in the development of the oncogenic phenotype [21, 46, 133, 134]. Such studies can be linked to other studies focusing on determining the effects of genes involved in carcinogen metabolism (detoxification and/or activation), redox enzymes, and DNA repair pathways [133]. Numerous SNPs associated with change of function have been identified in antioxidant enzymes including *CAT*, *GPX1*, *GSR*, and *SOD2* [21, 134]. Additionally, the association between genetic polymorphisms in genes with anti-tumor activity and those involved in the cell cycle has been reported in ovarian cancer [135, 136]. Recently, several genetic variations have been identified in genome-wide association studies (GWAS), and were found to act as low to moderate penetrant alleles, which contribute to ovarian cancer risk, as well as other diseases [23, 137].

There is now an association of specific SNPs in key oxidant and anti-oxidant enzymes with increased risk and overall survival of ovarian cancer [21, 46]. A common SNP that reduced *CAT* activity (rs1001179) was utilized as a significant predictor of death when present in ovarian cancer patients and was also associated with increased risk for breast cancer [21, 46, 134, 138]. This SNP is also linked to increased risk, survival, and response to adjuvant treatment of cancer patients, including ovarian [46, 139]. Another common SNP that reduced *CYBA* activity (rs4673) was also reported to be associated with an increased risk for ovarian cancer [21, 46]. The mutant genotype of the *CYBA* gene has been shown to both decrease and increase activity of the protein, thereby altering the generation of $O_2^{\bullet-}$ [21, 46]. Moreover, functionally distinct *MPO* polymorphisms, such as (rs2333227) have been linked to relative increased risk for development of ovarian cancer as well as other cancers [21, 44, 46]. Additional SNPs that influenced the risk of EOC have been successfully identified from the GWAS studies including rs3814113 (located at 9p22, near *BNC2*), rs2072590 (located at 2q31, which contains a family of *HOX* genes), rs2665390 (located at 3q25, intronic to *TIPARP*), rs10088218 (located at 8q24, 700 kb downstream of *MYC*), rs8170 (located at 19p13, near *MERIT40*), and rs9303542 (located at 17q21, intronic to *SKAP1*) [21, 46]. Thus, the genetic component of increased ovarian cancer risk may be attributed to SNPs that result in point mutations in the redox genes and potentially other genes [140].

11. Chemoresistance is associated with point mutations in key redox enzymes in EOC cells

To date, the acquisition of chemoresistance in ovarian cancer is not fully understood. The enhanced oxidant state reported in chemoresistant EOC cells may be linked to point mutations in key redox enzymes [21]. Chemoresistant EOC cells manifested increased levels of *CAT*, *GPX*, and *iNOS* and decreased levels of *GSR*, *SOD*, and *NAD(P)H* oxidase as compared to their sensitive counterparts [21]. Interestingly, chemoresistant EOC cells, and not their sensitive counterparts,

manifested specific point mutations that corresponded to known functional SNPs, in key redox enzymes including *SOD2* (rs4880), *NOS2* (rs2297518), and *CYBA* (rs4673) [1]. However, altered enzymatic activity for CAT and GSR observed in chemoresistant EOC cells did not correspond to the specific SNP of interest in those enzymes, indicating involvement of other possible functional SNPs for those enzymes [21]. Coincidentally, chemotherapy treatment induced point mutations that happen to correspond to known functional SNPs in key oxidant enzymes subsequently led to the acquisition of chemoresistance by EOC cells. Indeed, the induction of specific point mutations in *SOD2* or *GPX1* in sensitive EOC cells resulted in a decrease in the sensitivity to chemotherapy of these cells [21]. In fact, the addition of SOD to sensitive EOC cells during chemotherapy treatment synergistically increased the efficacy to chemotherapy [21].

Alternatively, the observed nucleotide switch in response to chemotherapy in EOC cells may be the result of nucleotide substitution, a process that includes transitions, replacement of one purine by the other or that of one pyrimidine by the other, or transversions, replacement of a purine by a pyrimidine or vice versa [21]. Indeed, hydroxyl radicals are known to react with DNA causing the formation of many pyrimidine and purine-derived lesions [21]. The oxidative damage to 8-Oxo-2'-deoxyguanosine, a major product of DNA oxidation, induces genetic alterations in oncogenes and tumor suppressor genes has been involved in tumor initiation and progression [21]. A GC to TA transversion has been reported in the *ras* oncogene and the *p53* tumor suppressor gene in several cancers. However, the GC to TA transversion is not unique to hydroxy-2'-deoxyguanosine, as CC to TT substitutions have been identified as signature mutations for oxidants and free radicals [21].

Moreover, the observed nucleotide switch in response to chemotherapy in EOC cells can be due to the fact that acquisition of chemoresistance generates an entirely different population of cells with a distinct genotype. Hence, chemotherapy kills the bulk of the tumor cells leaving a subtype of cancer cells with ability for repair and renewal, known as cancer stem cells (CSCs) [21]. Indeed, cancer stem cells have been isolated from various types of cancer including leukemia, breast, brain, pancreatic, prostate, ovarian and colon [21]. Interestingly, CSC populations were present in cultures of SKOV-3 EOC cells and have been shown to be chemoresistance in nature [21].

12. Further increasing pro-oxidant enzymes: potential survival mechanism

Apoptosis is a tightly regulated molecular process that removes excess or unwanted cells from organisms. Resistance to apoptosis is a key feature of cancer cells and is involved in the pathogenesis of cancer. We have previously reported that EOC cells have significantly increased levels of NO, which correlated with increased expression in iNOS [54]. We have also reported that EOC cells manifested lower apoptosis, which was markedly induced by inhibiting iNOS by L-NAME, indicating a strong link between apoptosis and NO/iNOS pathways in these cells [54]. Caspase-3 is known to play a critical role in controlling apoptosis, by participating in a cascade that is triggered in response to proapoptotic signals and culminates in cleavage of a set of

proteins, resulting in disassembly of the cell [141–144]. Caspase-3 was found to be S-nitrosylated on the catalytic-site cysteine in unstimulated human lymphocyte cell lines and denitrosylated upon activation of the Fas apoptotic pathway [145]. Decreased caspase-3 S-nitrosylation was associated with an increase in intracellular caspase activity. Caspase-3 S-nitrosylation/denitrosylation is known to serve as an on/off switch regulating caspase activity during apoptosis in endothelial cells, lymphocytes and trophoblasts [146–149]. The mechanisms underlying S-nitrosothiol (SNO) formation *in vivo* are not well understood.

Myeloperoxidase typically uses H_2O_2 in combination with chloride to generate hypochlorous acid [55, 150–153]. We, and others, have demonstrated that MPO utilizes NO, produced by iNOS, as a one-electron substrate generating NO^+ , a labile nitrosating species that is rapidly hydrolyzed forming nitrite as end-product [55, 56, 154, 155]. The ability of MPO to generate NO^+ from NO, led us to believe that not only does MPO play a role in S-nitrosylation of caspase-3 in EOC cells, but also highlights a possible cross-talk between iNOS and MPO. Indeed, we observed that MPO is responsible for the S-nitrosylation of caspase-3, which led to the inhibition of caspase-3 in EOC cells. Silencing MPO gene expression induced apoptosis in EOC cells through a mechanism that involved S-nitrosylation of caspase-3 by MPO.

Molecular alterations that lead to apoptosis can be inhibited by S-nitrosylation of apoptotic proteins such as caspases. Thus, S-nitrosylation conveys a key influence of NO on apoptosis signaling and may act as a key regulator for apoptosis in cancer cells. It has been known that the effects of NO on apoptosis are not only stimulatory but may also be inhibitory. These paradoxical effects of NO on apoptosis seem to be influenced by several factors. It has been suggested that biological conditions, such as the redox state, concentration, exposure time and the combination with O_2 , $O_2^{\bullet-}$ and other molecules, determines the net effect of NO on apoptosis [156]. Also, NO is implicated in both apoptotic and necrotic cell death depending on the NO chemistry and the cellular biological redox state [57, 156]. As described earlier, we have previously demonstrated that the EOC cell lines, SKOV-3 and MDAH-2774, manifested lower apoptosis and had significantly higher levels of NO due to the presence of elevated levels of iNOS [54, 157]. We have also reported significant levels of MPO expression, which was found to be co-localized with iNOS, in both EOC cell lines SKOV-3 and MDAH-2774 [53]. We have demonstrated that 65% of the invasive epithelial ovarian carcinoma specimens tested expressed MPO in the neoplastic cells. The co-localization of MPO and iNOS has been demonstrated by immunohistochemical studies in cytokine-treated human neutrophils and primary granules of activated leukocytes [158]. Both plasma levels and tissue expression of MPO in gynecologic malignancies were previously evaluated and it was found that gynecologic cancer patients had higher plasma MPO compared to control subjects [159]. Using immunostaining, it was also demonstrated that MPO expression was higher in cancer tissues compared to control [159].

We have now characterized chemoresistant EOC cells to manifest an even further increase in pro-oxidant enzymes including MPO, and NO, a surrogate for iNOS activity in conjunction with a further increase in the S-nitrosylation of caspase-3 (*data not published*) and a concurrent decrease in the level of apoptosis [21]. Thus, we hypothesized that the decrease in apoptosis observed in chemoresistant EOC cells is a consequence of a further increase in the degree of S-nitrosylation of caspase-3. Since resistance to apoptosis is a hallmark of tumor

growth, identifying mechanisms of this resistance such as S-nitrosylation may be a key in cancer progression and the development of chemoresistance. S-nitrosylation is reversible and seemingly a specific post-translational modification that regulates the activity of several signaling proteins. S-nitrosylation of the catalytic site cysteine in caspases serves as an on/off switch regulating caspase activity during apoptosis in endothelial cells, lymphocytes, and trophoblasts [147–149]. Targeting MPO may be a potential therapeutic intervention to reverse the resistance to apoptosis in sensitive and chemoresistant EOC cells.

13. Ovarian cancer immunotherapy and oxidative stress

It is well established that tumorigenic cells generate high levels of ROS to activate proximal signaling pathways that promote proliferation, survival and metabolic adaptation while also maintaining a high level of antioxidant activity to prevent buildup of ROS to levels that could induce cell death [160]. Moreover, there is evidence that ROS can act as secondary messengers in immune cells, which can lead to hyperactivation of inflammatory responses resulting in tissue damage and pathology [160]. Ovarian cancer is considered an ideal tumorigenic cancer because ovarian cancer cells have no negative impact on immune cells [161].

Effective immunotherapy for ovarian cancer is currently the focus of several investigations and clinical trials. Current immunotherapies for cancer treatment include therapeutic vaccines, cytokines, immune modulators, immune checkpoint inhibitors, and adoptive T cell transfer [162]. The discovery of a monoclonal antibodies (such as bevacizumab) directed against VEGF have been shown to improve progression free survival compared to cytotoxic chemotherapy alone was a major outcome of these clinical trials [163]. Other monoclonal antibodies currently approved for other cancers such as trastuzumab for breast cancer or cetuximab for colon cancer exhibited limited activity in ovarian cancer [163]. Several clinical trials are ongoing for the utilization of immune checkpoint blockade in ovarian cancer immune therapy [164]. Most recently tested were the programmed death (PD)-1 inhibitors, pembrolizumab and nivolumab, which showed a consistent response rate of 10–20% in phase 2 studies and then failed to improve outcomes in confirmatory trials [164]. Ultimately, larger phase 3 studies are needed to validate these findings for checkpoint inhibitors, particularly with regard to the duration of response seen with these agents. Additionally, the direct intraperitoneal delivery of interleukin (IL)-12, a potent immunostimulatory agent, exhibited some potential therapeutic efficacy in ovarian cancer [165]. Recently, targeting folate receptor alpha, which is found to be expressed in ovarian cancer, has shown promising therapeutic value. The targeting of the folate receptor was achieved by either a blocking monoclonal antibody (farletuzumab) or antibody conjugates of folate analogs, such as vintafolide [166].

14. Summary and conclusion

Oxidative stress has been implicated in the pathogenesis of several malignancies including ovarian cancer. Epithelial ovarian cancer is characterized to manifest a persistent pro-oxidant

state through alteration of the redox balance, which is further enhanced in their chemoresistant counterparts, as summarized in **Figure 2**. Forcing ovarian cancer cells to undergo oxidative phosphorylation rather than glycolysis has been shown to be beneficial for eliminating cells via apoptosis (**Figure 2**). Collectively, there is convincing evidence that indicated a causal relationship between the acquisition of chemoresistance and chemotherapy-induced genetic mutations in key redox enzymes, leading to a further enhanced oxidative stress in chemoresistant EOC cells. This concept was further confirmed by the observation that induction of point mutations in sensitive EOC cells increased their resistance to chemotherapy. Also, a combination of antioxidants with chemotherapy significantly sensitized cells to chemotherapy. Identification of targets for chemoresistance with either biomarker and/or screening potential will have a significant impact for the treatment of this disease.

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References

- [1] Saed GM, Diamond MP, Fletcher NM. Updates of the role of oxidative stress in the pathogenesis of ovarian cancer. *Gynecologic Oncology*. 2017;**145**(3):595-602
- [2] Rojas V et al. Molecular characterization of epithelial ovarian cancer: Implications for diagnosis and treatment. *International Journal of Molecular Sciences*. 2016;**17**(12)
- [3] Blagden SP. Harnessing pandemonium: The clinical implications of tumor heterogeneity in ovarian cancer. *Frontiers in Oncology*. 2015;**5**:149
- [4] Leahy Y. Are serum protein biomarkers effective in detecting ovarian cancer in its early stages? *Clinical Journal of Oncology Nursing*. 2009;**13**(4):443-445
- [5] Zhen W et al. Increased gene-specific repair of cisplatin interstrand cross-links in cisplatin-resistant human ovarian cancer cell lines. *Molecular and Cellular Biology*. 1992;**12**(9):3689-3698
- [6] Lee C, Macgregor P. Drug resistance and microarrays. *Modern Drug Discovery*. 2004;**7**(7)
- [7] Lippert TH, Ruoff HJ, Volm M. Current status of methods to assess cancer drug resistance. *International Journal of Medical Sciences*. 2011;**8**(3):245-253
- [8] Matsuo K et al. Clinical relevance of extent of extreme drug resistance in epithelial ovarian carcinoma. *Gynecologic Oncology*. 2010;**116**(1):61-65
- [9] Taddei ML et al. Mitochondrial oxidative stress due to complex I dysfunction promotes fibroblast activation and melanoma cell invasiveness. *Journal of Signal Transduction*. 2012;**2012**:684592
- [10] Hileman EO et al. Intrinsic oxidative stress in cancer cells: A biochemical basis for therapeutic selectivity. *Cancer Chemotherapy and Pharmacology*. 2004;**53**(3):209-219
- [11] Toyokuni S. Oxidative stress and cancer: The role of redox regulation. *Biotherapy*. 1998;**11**(2-3):147-154
- [12] Toyokuni S et al. Persistent oxidative stress in cancer. *FEBS Letters*. 1995;**358**(1):1-3
- [13] Reuter S et al. Oxidative stress, inflammation, and cancer: How are they linked? *Free Radical Biology & Medicine*. 2010;**49**(11):1603-1616
- [14] Beckman KB, Ames BN. The free radical theory of aging matures. *Physiological Reviews*. 1998;**78**(2):547-581
- [15] Choi JY et al. Iron intake, oxidative stress-related genes (MnSOD and MPO) and prostate cancer risk in CARET cohort. *Carcinogenesis*. 2008;**29**(5):964-970
- [16] Coussens LM, Werb Z. Inflammation and cancer. *Nature*. 2002;**420**(6917):860-867
- [17] Finkel T, Holbrook NJ. Oxidants, oxidative stress and the biology of ageing. *Nature*. 2000;**408**(6809):239-247

- [18] Erickson BK, Conner MG, Landen CN Jr. The role of the fallopian tube in the origin of ovarian cancer. *American Journal of Obstetrics and Gynecology*. 2013;**209**(5):409-414
- [19] Kurman RJ, Shih Ie M. The dualistic model of ovarian carcinogenesis: Revisited, revised, and expanded. *American Journal of Pathology*. 2016;**186**(4):733-747
- [20] Hibbs K et al. Differential gene expression in ovarian carcinoma: Identification of potential biomarkers. *The American Journal of Pathology*. 2004;**165**(2):397-414
- [21] Fletcher NM et al. Specific point mutations in key redox enzymes are associated with chemoresistance in epithelial ovarian cancer. *Free Radical Biology & Medicine*. 2016;**102**:122-132
- [22] Fletcher NM et al. Myeloperoxidase and free iron levels: Potential biomarkers for early detection and prognosis of ovarian cancer. *Cancer Biomarkers*. 2011;**10**(6):267-275
- [23] Ramus SJ et al. Consortium analysis of 7 candidate SNPs for ovarian cancer. *International Journal of Cancer*. 2008;**123**(2):380-388
- [24] Lengyel E. Ovarian cancer development and metastasis. *The American Journal of Pathology*. 2010;**177**(3):1053-1064
- [25] Liao J et al. Ovarian cancer spheroid cells with stem cell-like properties contribute to tumor generation, metastasis and chemotherapy resistance through hypoxia-resistant metabolism. *PLoS One*. 2014;**9**(1) e84941
- [26] Vermeersch KA et al. OVCAR-3 spheroid-derived cells display distinct metabolic profiles. *PLoS One*. 2015;**10**(2):e0118262
- [27] Lei XG et al. Paradoxical roles of antioxidant enzymes: Basic mechanisms and health implications. *Physiological Reviews*. 2016;**96**(1):307-364
- [28] Klaunig JE, Kamendulis LM, Hocevar BA. Oxidative stress and oxidative damage in carcinogenesis. *Toxicologic Pathology*. 2010;**38**(1):96-109
- [29] Fruehauf JP, Meyskens FL Jr. Reactive oxygen species: A breath of life or death? *Clinical Cancer Research*. 2007;**13**(3):789-794
- [30] Circu ML, Aw TY. Glutathione and modulation of cell apoptosis. *Biochimica et Biophysica Acta*. 2012;**1823**(10):1767-1777
- [31] Ishikawa T, Ali-Osman F. Glutathione-associated cis-diamminedichloroplatinum(II) metabolism and ATP-dependent efflux from leukemia cells. Molecular characterization of glutathione-platinum complex and its biological significance. *The Journal of Biological Chemistry*. 1993;**268**(27):20116-20125
- [32] Wang J, Yi J. Cancer cell killing via ROS: To increase or decrease, that is the question. *Cancer Biology & Therapy*. 2008;**7**(12):1875-1884
- [33] Schmidt HH et al. Antioxidants in translational medicine. *Antioxidants & Redox Signaling*. 2015;**23**(14):1130-1143

- [34] Waris G, Ahsan H. Reactive oxygen species: Role in the development of cancer and various chronic conditions. *Journal of Carcinogenesis*. 2006;**5**:14
- [35] Roos WP, Thomas AD, Kaina B. DNA damage and the balance between survival and death in cancer biology. *Nature Reviews. Cancer*. 2016;**16**(1):20-33
- [36] Retel J et al. Mutational specificity of oxidative DNA damage. *Mutation Research*. 1993;**299**(3-4):165-182
- [37] Westermarck J, Kahari VM. Regulation of matrix metalloproteinase expression in tumor invasion. *The FASEB Journal*. 1999;**13**(8):781-792
- [38] Mazure NM et al. Oncogenic transformation and hypoxia synergistically act to modulate vascular endothelial growth factor expression. *Cancer Research*. 1996;**56**(15):3436-3440
- [39] Okada F et al. Impact of oncogenes in tumor angiogenesis: Mutant K-ras up-regulation of vascular endothelial growth factor/vascular permeability factor is necessary, but not sufficient for tumorigenicity of human colorectal carcinoma cells. *Proceedings of the National Academy of Sciences of the United States of America*. 1998;**95**(7):3609-3614
- [40] Saed GM et al. Dichloroacetate induces apoptosis of epithelial ovarian cancer cells through a mechanism involving modulation of oxidative stress. *Reproductive Sciences*. 2011;**18**(12):1253-1261
- [41] Michelakis ED, Webster L, Mackey JR. Dichloroacetate (DCA) as a potential metabolic-targeting therapy for cancer. *British Journal of Cancer*. 2008;**99**(7):989-994
- [42] Bell EL, Emerling BM, Chandel NS. Mitochondrial regulation of oxygen sensing. *Mitochondrion*. 2005;**5**(5):322-332
- [43] Mansfield KD et al. Mitochondrial dysfunction resulting from loss of cytochrome c impairs cellular oxygen sensing and hypoxic HIF- α activation. *Cell Metabolism*. 2005;**1**(6):393-399
- [44] Castillo-Tong DC et al. Association of myeloperoxidase with ovarian cancer. *Tumour Biology*. 2014;**35**(1):141-148
- [45] Belotte J et al. The role of oxidative stress in the development of cisplatin resistance in epithelial ovarian cancer. *Reproductive Sciences*. 2013
- [46] Belotte J et al. A single nucleotide polymorphism in catalase is strongly associated with ovarian cancer survival. *PLoS One*. 2015;**10**(8):e0135739
- [47] Watson J. Oxidants, antioxidants and the current incurability of metastatic cancers. *Open Biology*. 2013;**3**(1):120144
- [48] Klein EA et al. Vitamin E and the risk of prostate cancer: The selenium and vitamin E cancer prevention trial (SELECT). *JAMA*. 2011;**306**(14):1549-1556
- [49] Bjelakovic G et al. Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: Systematic review and meta-analysis. *JAMA*. 2007;**297**(8):842-857

- [50] Sayin VI et al. Antioxidants accelerate lung cancer progression in mice. *Science Translational Medicine*. 2014;**6**(221) 221ra15
- [51] Senthil K, Aranganathan S, Nalini N. Evidence of oxidative stress in the circulation of ovarian cancer patients. *Clinica Chimica Acta*. 2004;**339**(1-2):27-32
- [52] Jiang Z et al. Modulation of redox signaling promotes apoptosis in epithelial ovarian cancer cells. *Gynecologic Oncology*. 2011;**122**(2):418-423
- [53] Saed GM et al. Myeloperoxidase serves as a redox switch that regulates apoptosis in epithelial ovarian cancer. *Gynecologic Oncology*. 2010;**116**(2):276-281
- [54] Malone JM et al. The effects of the inhibition of inducible nitric oxide synthase on angiogenesis of epithelial ovarian cancer. *American Journal of Obstetrics and Gynecology*. 2006;**194**(4):1110-6; discussion 1116-8
- [55] Abu-Soud HM, Hazen SL. Nitric oxide is a physiological substrate for mammalian peroxidases. *The Journal of Biological Chemistry*. 2000;**275**(48):37524-37532
- [56] Abu-Soud HM, Hazen SL. Nitric oxide modulates the catalytic activity of myeloperoxidase. *The Journal of Biological Chemistry*. 2000;**275**(8):5425-5430
- [57] Habib S, Ali A. Biochemistry of nitric oxide. *Indian Journal of Clinical Biochemistry*. 2011;**26**(1):3-17
- [58] Muscat JE, Huncharek MS. Perineal talc use and ovarian cancer: A critical review. *European Journal of Cancer Prevention*. 2008;**17**(2):139-146
- [59] Sasaroli D, Coukos G, Scholler N. Beyond CA125: The coming of age of ovarian cancer biomarkers. Are we there yet? *Biomarkers in Medicine*. 2009;**3**(3):275-288
- [60] Schummer M et al. Comparative hybridization of an array of 21,500 ovarian cDNAs for the discovery of genes overexpressed in ovarian carcinomas. *Gene*. 1999;**238**(2):375-385
- [61] Drapkin R et al. Human epididymis protein 4 (HE4) is a secreted glycoprotein that is overexpressed by serous and endometrioid ovarian carcinomas. *Cancer Research*. 2005;**65**(6):2162-2169
- [62] Galgano MT, Hampton GM, Frierson HF Jr. Comprehensive analysis of HE4 expression in normal and malignant human tissues. *Modern Pathology*. 2006;**19**(6):847-853
- [63] Gilks CB et al. Distinction between serous tumors of low malignant potential and serous carcinomas based on global mRNA expression profiling. *Gynecologic Oncology*. 2005;**96**(3):684-694
- [64] Hough CD et al. Large-scale serial analysis of gene expression reveals genes differentially expressed in ovarian cancer. *Cancer Research*. 2000;**60**(22):6281-6287
- [65] Bouchard D et al. Proteins with whey-acidic-protein motifs and cancer. *The Lancet Oncology*. 2006;**7**(2):167-174
- [66] Rosen DG et al. Potential markers that complement expression of CA125 in epithelial ovarian cancer. *Gynecologic Oncology*. 2005;**99**(2):267-277

- [67] Scholler N et al. Bead-based ELISA for validation of ovarian cancer early detection markers. *Clinical Cancer Research*. 2006;**12**(7 Pt 1):2117-2124
- [68] Moore RG et al. The use of multiple novel tumor biomarkers for the detection of ovarian carcinoma in patients with a pelvic mass. *Gynecologic Oncology*. 2008;**108**(2):402-408
- [69] Kim JW, Dang CV. Multifaceted roles of glycolytic enzymes. *Trends in Biochemical Sciences*. 2005;**30**(3):142-150
- [70] Menon U et al. Prospective study using the risk of ovarian cancer algorithm to screen for ovarian cancer. *Journal of Clinical Oncology*. 2005;**23**(31):7919-7926
- [71] Xu FJ et al. OVX1 as a marker for early stage endometrial carcinoma. *Cancer*. 1994;**73**(7):1855-1858
- [72] Havrilesky LJ et al. Evaluation of biomarker panels for early stage ovarian cancer detection and monitoring for disease recurrence. *Gynecologic Oncology*. 2008;**110**(3):374-382
- [73] Loria V et al. Myeloperoxidase: A new biomarker of inflammation in ischemic heart disease and acute coronary syndromes. *Mediators of Inflammation*. 2008;**2008**:135625
- [74] Dally H et al. Myeloperoxidase (MPO) genotype and lung cancer histologic types: The MPO -463 a allele is associated with reduced risk for small cell lung cancer in smokers. *International Journal of Cancer*. 2002;**102**(5):530-535
- [75] Ekmekci OB et al. Iron, nitric oxide, and myeloperoxidase in asthmatic patients. *Biochemistry (Mosc)*. 2004;**69**(4):462-467
- [76] Baldus S et al. Myeloperoxidase serum levels predict risk in patients with acute coronary syndromes. *Circulation*. 2003;**108**(12):1440-1445
- [77] Brennan ML et al. Prognostic value of myeloperoxidase in patients with chest pain. *The New England Journal of Medicine*. 2003;**349**(17):1595-1604
- [78] Muscara MN et al. Wound collagen deposition in rats: Effects of an NO-NSAID and a selective COX-2 inhibitor. *British Journal of Pharmacology*. 2000;**129**(4):681-686
- [79] Shi HP et al. The role of iNOS in wound healing. *Surgery*. 2001;**130**(2):225-229
- [80] Witte MB, Barbul A. Role of nitric oxide in wound repair. *American Journal of Surgery*. 2002;**183**(4):406-412
- [81] Sadrzadeh SM et al. Hemoglobin. A biologic fenton reagent. *The Journal of Biological Chemistry*. 1984;**259**(23):14354-14356
- [82] Galijasevic S et al. Myeloperoxidase interaction with peroxynitrite: Chloride deficiency and heme depletion. *Free Radical Biology & Medicine*. 2009;**47**(4):431-439
- [83] Maitra D et al. Melatonin can mediate its vascular protective effect by modulating free iron level by inhibiting hypochlorous acid-mediated hemoprotein heme destruction. *Hypertension*. 2011;**57**(5):e22 author reply e23

- [84] Maitra D et al. Reaction of hemoglobin with HOCl: Mechanism of heme destruction and free iron release. *Free Radical Biology & Medicine*. 2011;**51**(2):374-386
- [85] Maitra D et al. Mechanism of hypochlorous acid-mediated heme destruction and free iron release. *Free Radical Biology & Medicine*. 2011;**51**(2):364-373
- [86] Bozzini C et al. Biochemical and genetic markers of iron status and the risk of coronary artery disease: An angiography-based study. *Clinical Chemistry*. 2002;**48**(4):622-628
- [87] de Valk B, Marx JJ. Iron, atherosclerosis, and ischemic heart disease. *Archives of Internal Medicine*. 1999;**159**(14):1542-1548
- [88] Sullivan JL. Iron and the genetics of cardiovascular disease. *Circulation*. 1999;**100**(12):1260-1263
- [89] Niederau C. Iron overload and atherosclerosis. *Hepatology*. 2000;**32**(3):672-674
- [90] Brault S et al. Lysophosphatidic acid induces endothelial cell death by modulating the redox environment. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology*. 2007;**292**(3):R1174-R1183
- [91] O'Donnell BV et al. Studies on the inhibitory mechanism of iodonium compounds with special reference to neutrophil NADPH oxidase. *The Biochemical Journal*. 1993;**290** (Pt 1):41-49
- [92] Park SE et al. Diphenyliodonium induces ROS-independent p53 expression and apoptosis in human RPE cells. *FEBS Letters*. 2007;**581**(2):180-186
- [93] Boveris A, Chance B. The mitochondrial generation of hydrogen peroxide. General properties and effect of hyperbaric oxygen. *The Biochemical Journal*. 1973;**134**(3):707-716
- [94] Volm M, Koomagi R. Hypoxia-inducible factor (HIF-1) and its relationship to apoptosis and proliferation in lung cancer. *Anticancer Research*. 2000;**20**(3A):1527-1533
- [95] Tanaka M et al. Anti-metastatic gene therapy utilizing subcutaneous inoculation of EC-SOD gene transduced autologous fibroblast suppressed lung metastasis of meth-a cells and 3LL cells in mice. *Gene Therapy*. 2001;**8**(2):149-156
- [96] Wheeler MD, Smutney OM, Samulski RJ. Secretion of extracellular superoxide dismutase from muscle transduced with recombinant adenovirus inhibits the growth of B16 melanomas in mice. *Molecular Cancer Research*. 2003;**1**(12):871-881
- [97] Suliman HB, Ali M, Piantadosi CA. Superoxide dismutase-3 promotes full expression of the EPO response to hypoxia. *Blood*. 2004;**104**(1):43-50
- [98] Arbiser JL et al. Reactive oxygen generated by Nox1 triggers the angiogenic switch. *Proceedings of the National Academy of Sciences of the United States of America*. 2002;**99**(2):715-720
- [99] Pelicano H, Carney D, Huang P. ROS stress in cancer cells and therapeutic implications. *Drug Resistance Updates*. 2004;**7**(2):97-110

- [100] Trachootham D, Alexandre J, Huang P. Targeting cancer cells by ROS-mediated mechanisms: A radical therapeutic approach? *Nature Reviews. Drug Discovery*. 2009; **8**(7):579-591
- [101] Desouki MM et al. Cross talk between mitochondria and superoxide generating NADPH oxidase in breast and ovarian tumors. *Cancer Biology & Therapy*. 2005; **4**(12):1367-1373
- [102] Mochizuki T et al. Inhibition of NADPH oxidase 4 activates apoptosis via the AKT/apoptosis signal-regulating kinase 1 pathway in pancreatic cancer PANC-1 cells. *Oncogene*. 2006; **25**(26):3699-3707
- [103] Mabuchi S et al. Estrogen inhibits paclitaxel-induced apoptosis via the phosphorylation of apoptosis signal-regulating kinase 1 in human ovarian cancer cell lines. *Endocrinology*. 2004; **145**(1):49-58
- [104] Wang X et al. Epidermal growth factor receptor-dependent Akt activation by oxidative stress enhances cell survival. *The Journal of Biological Chemistry*. 2000; **275**(19):14624-14631
- [105] Piret JP et al. CoCl₂, a chemical inducer of hypoxia-inducible factor-1, and hypoxia reduce apoptotic cell death in hepatoma cell line HepG2. *Annals of the New York Academy of Sciences*. 2002; **973**:443-447
- [106] Li Y, Trush MA. Diphenyleneiodonium, an NAD(P)H oxidase inhibitor, also potently inhibits mitochondrial reactive oxygen species production. *Biochemical and Biophysical Research Communications*. 1998; **253**(2):295-299
- [107] Shi Y et al. Rapamycin enhances apoptosis and increases sensitivity to cisplatin in vitro. *Cancer Research*. 1995; **55**(9):1982-1988
- [108] Scaife RM. Selective and irreversible cell cycle inhibition by diphenyleneiodonium. *Molecular Cancer Therapeutics*. 2005; **4**(6):876-884
- [109] Goud AP et al. Reactive oxygen species and oocyte aging: Role of superoxide, hydrogen peroxide, and hypochlorous acid. *Free Radical Biology & Medicine*. 2008; **44**(7):1295-1304
- [110] McCord JM, Fridovich I. Superoxide dismutase. An enzymic function for erythrocyte hemocuprein (hemocuprein). *The Journal of Biological Chemistry*. 1969; **244**(22):6049-6055
- [111] Schallreuter KU et al. In vivo and in vitro evidence for hydrogen peroxide (H₂O₂) accumulation in the epidermis of patients with vitiligo and its successful removal by a UVB-activated pseudocatalase. *The Journal of Investigative Dermatology. Symposium Proceedings*. 1999; **4**(1):91-96
- [112] Hu Y et al. Mitochondrial manganese-superoxide dismutase expression in ovarian cancer: Role in cell proliferation and response to oxidative stress. *The Journal of Biological Chemistry*. 2005; **280**(47):39485-39492
- [113] Calastretti A et al. Damaged microtubules can inactivate BCL-2 by means of the mTOR kinase. *Oncogene*. 2001; **20**(43):6172-6180

- [114] Jiang H, Feng Y. Hypoxia-inducible factor 1alpha (HIF-1alpha) correlated with tumor growth and apoptosis in ovarian cancer. *International Journal of Gynecological Cancer*. 2006;**16**(Suppl 1):405-412
- [115] Kaewpila S et al. Manganese superoxide dismutase modulates hypoxia-inducible factor-1 alpha induction via superoxide. *Cancer Research*. 2008;**68**(8):2781-2788
- [116] Chen B et al. Roles of microRNA on cancer cell metabolism. *Journal of Translational Medicine*. 2012;**10**:228
- [117] Vander Heiden MG et al. Evidence for an alternative glycolytic pathway in rapidly proliferating cells. *Science*. 2010;**329**(5998):1492-1499
- [118] Kroemer G, Pouyssegur J. Tumor cell metabolism: cancer's Achilles' heel. *Cancer Cell*. 2008;**13**(6):472-482
- [119] Kim JW et al. HIF-1-mediated expression of pyruvate dehydrogenase kinase: A metabolic switch required for cellular adaptation to hypoxia. *Cell Metabolism*. 2006;**3**(3):177-185
- [120] Xie J et al. Dichloroacetate shifts the metabolism from glycolysis to glucose oxidation and exhibits synergistic growth inhibition with cisplatin in HeLa cells. *International Journal of Oncology*. 2011;**38**(2):409-417
- [121] Stacpoole PW et al. Evaluation of long-term treatment of children with congenital lactic acidosis with dichloroacetate. *Pediatrics*. 2008;**121**(5):e1223-e1228
- [122] Stacpoole PW. The pharmacology of dichloroacetate. *Metabolism*. 1989;**38**(11):1124-1144
- [123] Stockwin LH et al. Sodium dichloroacetate selectively targets cells with defects in the mitochondrial ETC. *International Journal of Cancer*. 2010;**127**(11):2510-2519
- [124] Kim JW, Dang CV. Cancer's molecular sweet tooth and the Warburg effect. *Cancer Research*. 2006;**66**(18):8927-8930
- [125] Xu RH et al. Inhibition of glycolysis in cancer cells: A novel strategy to overcome drug resistance associated with mitochondrial respiratory defect and hypoxia. *Cancer Research*. 2005;**65**(2):613-621
- [126] Kinnula VL, Crapo JD. Superoxide dismutases in malignant cells and human tumors. *Free Radical Biology & Medicine*. 2004;**36**(6):718-744
- [127] Tandon R et al. Oxidative stress in patients with essential hypertension. *National Medical Journal of India*. 2005;**18**(6):297-299
- [128] Storz P. Reactive oxygen species in tumor progression. *Frontiers in Bioscience*. 2005;**10**:1881-1896
- [129] Kajiyama H et al. Survival benefit of taxane plus platinum in recurrent ovarian cancer with non-clear cell, non-mucinous histology. *Journal of Gynecologic Oncology*. 2014;**25**(1):43-50

- [130] Landriscina M et al. Adaptation to oxidative stress, chemoresistance, and cell survival. *Antioxidants & Redox Signaling*. 2009;**11**(11):2701-2716
- [131] Traverso N et al. Role of glutathione in cancer progression and chemoresistance. *Oxidative Medicine and Cellular Longevity*. 2013;**2013**:972913
- [132] Erichsen HC, Chanock SJ. SNPs in cancer research and treatment. *British Journal of Cancer*. 2004;**90**(4):747-751
- [133] Klaunig JE et al. Oxidative stress and oxidative damage in chemical carcinogenesis. *Toxicology and Applied Pharmacology*. 2011;**254**(2):86-99
- [134] Forsberg L et al. A common functional C-T substitution polymorphism in the promoter region of the human catalase gene influences transcription factor binding, reporter gene transcription and is correlated to blood catalase levels. *Free Radical Biology & Medicine*. 2001;**30**(5):500-505
- [135] Goode EL et al. Candidate gene analysis using imputed genotypes: Cell cycle single-nucleotide polymorphisms and ovarian cancer risk. *Cancer Epidemiology, Biomarkers & Prevention*. 2009;**18**(3):935-944
- [136] Notaridou M et al. Common alleles in candidate susceptibility genes associated with risk and development of epithelial ovarian cancer. *International Journal of Cancer*. 2011;**128**(9):2063-2074
- [137] Savas S et al. Functional nsSNPs from carcinogenesis-related genes expressed in breast tissue: Potential breast cancer risk alleles and their distribution across human populations. *Human Genomics*. 2006;**2**(5):287-296
- [138] Quick SK et al. Effect modification by catalase genotype suggests a role for oxidative stress in the association of hormone replacement therapy with postmenopausal breast cancer risk. *Cancer Epidemiology, Biomarkers & Prevention*. 2008;**17**(5):1082-1087
- [139] Didziapetriene J et al. Significance of blood serum catalase activity and malondialdehyde level for survival prognosis of ovarian cancer patients. *Medicina (Kaunas, Lithuania)*. 2014;**50**(4):204-208
- [140] Sellers TA et al. Association of single nucleotide polymorphisms in glycosylation genes with risk of epithelial ovarian cancer. *Cancer Epidemiology, Biomarkers & Prevention*. 2008;**17**(2):397-404
- [141] Porter AG, Janicke RU. Emerging roles of caspase-3 in apoptosis. *Cell Death and Differentiation*. 1999;**6**(2):99-104
- [142] Liu L, Stamlor JS. NO: An inhibitor of cell death. *Cell Death and Differentiation*. 1999;**6**(10):937-942
- [143] Dimmeler S et al. Suppression of apoptosis by nitric oxide via inhibition of interleukin-1 β -converting enzyme (ICE)-like and cysteine protease protein (CPP)-32-like proteases. *The Journal of Experimental Medicine*. 1997;**185**(4):601-607

- [144] Thornberry NA, Lazebnik Y. Caspases: Enemies within. *Science*. 1998;**281**(5381):1312-1316
- [145] Mannick JB et al. Fas-induced caspase denitrosylation. *Science*. 1999;**284**(5414):651-654
- [146] Maejima Y et al. Nitric oxide inhibits myocardial apoptosis by preventing caspase-3 activity via S-nitrosylation. *Journal of Molecular and Cellular Cardiology*. 2005;**38**(1):163-174
- [147] Rossig L et al. Nitric oxide inhibits caspase-3 by S-nitrosation in vivo. *The Journal of Biological Chemistry*. 1999;**274**(11):6823-6826
- [148] Dash PR et al. Nitric oxide protects human extravillous trophoblast cells from apoptosis by a cyclic GMP-dependent mechanism and independently of caspase 3 nitrosylation. *Experimental Cell Research*. 2003;**287**(2):314-324
- [149] Mannick JB et al. S-Nitrosylation of mitochondrial caspases. *The Journal of Cell Biology*. 2001;**154**(6):1111-1116
- [150] Harrison JE, Schultz J. Studies on the chlorinating activity of myeloperoxidase. *The Journal of Biological Chemistry*. 1976;**251**(5):1371-1374
- [151] Kettle AJ, van Dalen CJ, Winterbourn CC. Peroxynitrite and myeloperoxidase leave the same footprint in protein nitration. *Redox Report*. 1997;**3**(5-6):257-258
- [152] Weiss SJ et al. Chlorination of taurine by human neutrophils. Evidence for hypochlorous acid generation. *Journal of Clinical Investigation*. 1982;**70**(3):598-607
- [153] Ortiz de Montellano PR. Catalytic sites of hemoprotein peroxidases. *Annual Review of Pharmacology and Toxicology*. 1992;**32**:89-107
- [154] Stamler JS, Singel DJ, Loscalzo J. Biochemistry of nitric oxide and its redox-activated forms. *Science*. 1992;**258**(5090):1898-1902
- [155] Abu-Soud HM et al. Peroxidases inhibit nitric oxide (NO) dependent bronchodilation: Development of a model describing NO-peroxidase interactions. *Biochemistry*. 2001;**40**(39):11866-11875
- [156] Nicotera P, Melino G. Regulation of the apoptosis-necrosis switch. *Oncogene*. 2004;**23**(16):2757-2765
- [157] Munkarah AR et al. Effects of prostaglandin E(2) on proliferation and apoptosis of epithelial ovarian cancer cells. *Journal of the Society for Gynecologic Investigation*. 2002;**9**(3):168-173
- [158] Evans TJ et al. Cytokine-treated human neutrophils contain inducible nitric oxide synthase that produces nitration of ingested bacteria. *Proceedings of the National Academy of Sciences of the United States of America*. 1996;**93**(18):9553-9558
- [159] Song M, Santanam N. Increased myeloperoxidase and lipid peroxide-modified protein in gynecological malignancies. *Antioxidants & Redox Signaling*. 2001;**3**(6):1139-1146

- [160] Schieber M, Chandel NS. ROS function in redox signaling and oxidative stress. *Current Biology*. 2014;**24**(10):R453-R462
- [161] Kandalaft LE et al. Immunotherapy for ovarian cancer: what's next? *Journal of Clinical Oncology*. 2011;**29**(7):925-933
- [162] De Felice F et al. Immunotherapy of ovarian cancer: The role of checkpoint inhibitors. *Journal of Immunology Research*. 2015;**2015**:191832
- [163] Zand B, Coleman RL, Sood AK. Targeting angiogenesis in gynecologic cancers. *Hematology/Oncology Clinics of North America*. 2012;**26**(3):543-563 viii
- [164] Chester C et al. Immunotherapeutic approaches to ovarian cancer treatment. *Journal of Immunotherapy Cancer*. 2015;**3**:7
- [165] Alvarez RD et al. A phase II trial of intraperitoneal EGEN-001, an IL-12 plasmid formulated with PEG-PEI-cholesterol lipopolymer in the treatment of persistent or recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer: A gynecologic oncology group study. *Gynecologic Oncology*. 2014;**133**(3):433-438
- [166] Marchetti C et al. Targeted drug delivery via folate receptors in recurrent ovarian cancer: A review. *Oncology Targets Therapy*. 2014;**7**:1223-1236

Exhibit 38

Alterations in Gene Expression in Human Mesothelial Cells Correlate with Mineral Pathogenicity

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Human mesothelial cells (LP9/TERT-1) were exposed to low and high (15 and 75 $\mu\text{m}^2/\text{cm}^2$ dish) equal surface area concentrations of crocidolite asbestos, nonfibrous talc, fine titanium dioxide (TiO_2), or glass beads for 8 or 24 hours. RNA was then isolated for Affymetrix microarrays, GeneSifter analysis and QRT-PCR. Gene changes by asbestos were concentration- and time-dependent. At low nontoxic concentrations, asbestos caused significant changes in mRNA expression of 29 genes at 8 hours and of 205 genes at 24 hours, whereas changes in mRNA levels of 236 genes occurred in cells exposed to high concentrations of asbestos for 8 hours. Human primary pleural mesothelial cells also showed the same patterns of increased gene expression by asbestos. Nonfibrous talc at low concentrations in LP9/TERT-1 mesothelial cells caused increased expression of 1 gene Activating Transcription Factor 3 (*ATF3*) at 8 hours and no changes at 24 hours, whereas expression levels of 30 genes were elevated at 8 hours at high talc concentrations. Fine TiO_2 or glass beads caused no changes in gene expression. In human ovarian epithelial (IOSE) cells, asbestos at high concentrations elevated expression of two genes (*NR4A2*, *MIP2*) at 8 hours and 16 genes at 24 hours that were distinct from those elevated in mesothelial cells. Since *ATF3* was the most highly expressed gene by asbestos, its functional importance in cytokine production by LP9/TERT-1 cells was assessed using siRNA approaches. Results reveal that *ATF3* modulates production of inflammatory cytokines (IL-1 β , IL-13, G-CSF) and growth factors (VEGF and PDGF-BB) in human mesothelial cells.

Keywords: mesothelioma; crocidolite asbestos; talc; titanium dioxide; gene profiling

A myriad of natural and synthetic fibers and particles, including nanomaterials, are being introduced into the workplace and environment, and *in vitro* screening tests on human cell types are needed to predict their toxicity and mechanisms of action, especially in target cells of disease. Asbestos is a group of well-characterized fibrous minerals that are associated with the development of nonmalignant (asbestosis) and malignant (lung cancers, pleural, and peritoneal mesotheliomas) diseases in occupational cohorts (1–3), yet the molecular mechanisms of asbestos-related diseases are poorly understood. Although it is widely acknowledged that fibrous geometry, surface and chemical composition, and durability are important features in the development

CLINICAL RELEVANCE

Results of work here suggest that transcriptional profiling can be used to reveal molecular events by mineral dusts that are predictive of their pathogenicity in mesothelioma.

of asbestos-associated diseases, how these contribute to cell toxicity and transformation are unclear. Moreover, the early molecular events leading to injury by asbestos fibers and other pathogenic or innocuous particulates in human cells that may be targets for the development of disease remain enigmatic.

The objective of work here was to compare acute toxicity and gene expression profiles of crocidolite asbestos, the type of asbestos most pathogenic in the causation of human mesothelioma (3, 4), to nonfibrous talc, fine titanium dioxide (TiO_2), and glass beads in a contact-inhibited, hTERT-immortalized human mesothelial cell line (5). In comparative studies, we also evaluated toxicity of particulates and gene expression changes in a contact-inhibited SV40 Tag-immortalized human ovarian epithelial cell line (IOSE) (6). This cell type is not implicated in asbestos-induced diseases, but is occasionally linked to inflammation and the development of ovarian cancer after use of talcum powder in the pelvic region, although such links are highly controversial (7).

Although most studies have evaluated the biological effects of particles and fibers on an equal mass or weight basis, the number, surface area, and reactivity of particulates at equal weight concentrations may be vastly different. Moreover, recent *in vitro* (8, 9) and *in vivo* (10–12), studies have confirmed that toxicity, oxidative stress, and inflammatory effects of ultrafine and other particles are related directly to surface area. For these reasons, and to avoid possible confounding alterations in gene expression or toxicity that might reflect or be masked in cells in different phases of the cell cycle, we introduced particulates at equal surface areas to confluent monolayers of human mesothelial (LP9/TERT-1) and human ovarian epithelial (IOSE) cells in a maintenance medium. Moreover, our studies included a nonfibrous talc sample and fine TiO_2 and glass particles, both traditionally used as nontoxic and nonpathogenic control particles in *in vitro* and animal experiments (reviewed in Refs. 13 and 14). Our studies provide novel insight into the early molecular events and responses occurring in human cells after exposure to asbestos and these materials.

MATERIALS AND METHODS

Human Mesothelial and Ovarian Epithelial Cell Cultures

Human mesothelial LP9/TERT-1 (LP9) cells, an hTERT-immortalized cell line phenotypically and functionally resembling normal human mesothelial cells (5), were obtained from Dr. James Rheinwald (Dana Farber Cancer Research Institute, Boston, MA). Human pleural mesothelial cells (NYU474) were isolated surgically from

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cancer-free patients by Dr. Harvey Pass (New York University, New York, NY). Briefly, tissue sample $2 \times 2 \text{ cm}^2$ was harvested into saline solution and rinsed immediately with PBS (1 \times) and Dulbecco's modified Eagle's medium (DMEM) (1 \times). The tissue was then digested with 0.2% Collagenase type 1 (MP Biomedical Inc., Solon, OH) for 3 hours at 37°C. Finally, the digested tissue was scraped and cells collected were centrifuged for 5 minutes at $300 \times g$. The cell pellet thus obtained was resuspended in DMEM containing 10% fetal bovine serum (FBS) and 2% penicillin–streptomycin, transferred into 6-well plate, and allowed to grow at 5% CO₂ and 37°C. Mesothelial cells were characterized by staining with calretinin antibody. An SV40 Tag-immortalized, anchorage-dependent human ovarian epithelial cell line (IOSE 398) (6) was a kind gift from Dr. Nelly Auersperg (Canadian Ovarian Tissue Bank, University of British Columbia, Vancouver, BC, Canada). LP9/TERT-1 cells were maintained in 50:50 DMEM/F-12 medium containing 10% FBS, and supplemented with penicillin (50 units/ml), streptomycin (100 $\mu\text{g/ml}$), hydrocortisone (100 $\mu\text{g/ml}$), insulin (2.5 $\mu\text{g/ml}$), transferrin (2.5 $\mu\text{g/ml}$), and selenium (2.5 $\mu\text{g/ml}$). IOSE cells were maintained in 50:50 199/MB105 medium containing 10% FBS and 50 $\mu\text{g/ml}$ gentamicin. Cells at near confluence were switched to maintenance medium containing 0.5% FBS for 24 hours before particulate exposure. NYU474 cells were grown to near confluence in DMEM containing 10% FBS and supplemented with penicillin (50 units/ml) and streptomycin (100 $\mu\text{g/ml}$).

Characterization of Mineral Preparations

The physical and chemical characterization of the NIEHS reference sample of crocidolite asbestos has been reported previously (15). The surface area of asbestos fibers and particles was measured using nitrogen gas sorption analysis to allow computation of identical amounts of surface areas of particulates to be added to cells. Fiber and particle size dimensions were determined by scanning electron microscopy (SEM) as described previously (16). In addition, talc was examined using field emission scanning electron microscopy (FESEM) and transmission electron microscopy (TEM). The chemical composition, surface area, mean size, and source of each particulate preparation is presented in Table 1.

Introduction of Particulates to Cells

After sterilization under ultraviolet light overnight to avoid endotoxin and microbial contamination, particulates were suspended in HBSS at 1 mg/ml, sonicated for 15 minutes in a water bath sonicator, and triturated five times through a 22-gauge needle. This suspension was added to cells in medium.

SEM to Determine Particulate/Cell Interactions

Cells were grown on Thermanox plastic cover slips (Nalge Nunc International, Naperville, IL), exposed to particulates for 24 hours, and then processed for SEM as described previously (16). After samples were critical point-dried, they were mounted on aluminum specimen stubs and dried before being sputter-coated with gold and palladium in a Polaron sputter coater (Model 5100; Quorum Technologies, Guelph, ON, Canada) and examined on a JSM 6060 scanning electron microscope (JEOL USA, Inc., Peabody, MA).

Cell Viability Studies

After 24 hours, cells were collected with Accutase cell detachment reagent, and final cell suspensions in Accutase/complete medium/HBSS

were mixed with 0.4% trypan blue stain, which is retained by dead cells. After 5 minutes, unstained cells were counted using a hemocytometer to determine the total number of viable cells per dish.

Based on the results of cell viability studies, asbestos and nonfibrous talc were evaluated in LP9 mesothelial cells for changes in gene expression at both low and high concentrations (15 and 75 $\mu\text{m}^2/\text{cm}^2$ dish) at 8 hours, and at low concentrations of minerals (15 $\mu\text{m}^2/\text{cm}^2$ dish) at 24 hours. These concentrations did not cause morphologic or toxic cellular changes at these time points. Negative control groups included cells exposed to fine TiO₂ (15 $\mu\text{m}^2/\text{cm}^2$ dish) at 8 and 24 hours and glass beads (75 $\mu\text{m}^2/\text{cm}^2$) at 24 hours. In IOSE cells, gene expression of all particulates was evaluated at 75 $\mu\text{m}^2/\text{cm}^2$ at 8 and 24 hours, as preliminary experiments revealed that no significant changes in mRNA levels were observed at 15 $\mu\text{m}^2/\text{cm}^2$ dish of asbestos. In NYU474 human mesothelial cells, QRT-PCR was used to validate a selected subset of gene expression changes identified by arrays in LP9/TERT-1 cells. Cells were exposed to 15 and 75 $\mu\text{m}^2/\text{cm}^2$ asbestos for 24 hours, and 8 genes highly expressed in LP9 cells were examined by QRT-PCR (see below).

RNA Preparation

Total RNA was prepared using an RNeasy Plus Mini Kit according to the manufacturers' protocol (Qiagen, Valencia, CA), as previously described (17).

Affymetrix Gene Profiling

Microarrays were performed on samples from three independent experiments. All cell types, time points, and mineral types and concentrations were included in all three experiments. For each experiment, $n = 3$ dishes were pooled into one sample per treatment group. Each of the pooled samples was analyzed on a separate array (i.e., $n = 3$ arrays per condition [3 independent biological replicates]). All procedures were performed by the Vermont Cancer Center DNA facility using standard Affymetrix protocol as previously described (14, 17). Each probe array, Human U133A 2.0 (Affymetrix, Santa Clara, CA) was scanned twice (Hewlett-Packard GeneArray Scanner, Palo Alto, CA), the images overlaid, and the average intensities of each probe cell compiled. Microarray data were analyzed using GeneSifter software (VizX Labs, Seattle, WA). This program used a “ t test” for pairwise comparison and a Benjamini-Hochberg test for false discovery rate (FDR 5%) to adjust for multiple comparisons. A 2-fold cutoff limit was used for analysis.

Quantitative Real-Time PCR

Total RNA (1 μg) was reverse-transcribed with random primers using the Promega AMV Reverse Transcriptase kit (Promega, Madison, WI) according to the recommendations of the manufacturer, as described previously (17). In NYU474 mesothelial cells, eight genes (*ATF3*, *SOD2*, *PTGS2*, *FOSB*, *TFPI2*, *PDGF4*, *NR4A2*, and *IL-8*) most highly expressed in LP9 cells were evaluated using the $\Delta\Delta\text{Ct}$ method. Duplicate or triplicate assays were performed with RNA samples isolated from at least three independent experiments. The values obtained from cDNAs and hypoxanthine phosphoribosyl transferase (*hprt*) controls provided relative gene expression levels for the gene locus investigated. The primers and probes used to validate gene expression as observed in microarrays were purchased from Applied Biosystems (Foster City, CA).

TABLE 1. CHARACTERIZATION OF PARTICULATES

Name	Chemical Composition	Mean Surface Area \pm SE (m^2/g)	Mean Size (μm)*	Source
Crocidolite Asbestos	$\text{Na}_2\text{Fe}_3^{2+}\text{Fe}_2^{3+}\text{Si}_8\text{O}_{22}(\text{OH})_2$	14.97 ± 0.605	7.4×0.25	NIEHS Reference Sample
Talc (MP 10-52) [†]	$\text{Mg}_3\text{Si}_4\text{O}_{10}(\text{OH})_2$	16.03 ± 0.654	1.1	Barrett's Minerals, Inc.
Titanium Dioxide	TiO ₂	9.02 ± 0.185	0.69	Fisher Scientific
Glass Beads	SiO ₂	2.78 ± 0.215	2.06	Polysciences Inc.

* Length \times width for crocidolite asbestos, and diameter for nonfibrous talc, TiO₂, and glass beads.

[†] Although standard reference samples of asbestos and some particulates are available for use by the scientific community, reference samples of talc currently do not exist. For these reasons, the nonfibrous talc sample was also characterized for physical properties, particle size distribution (0.70 μm minimum to 1.20 μm maximum), and chemical/mineralogical (talc 95%, chlorite 4.5–5%, dolomite 0.3%) composition. For complete analysis or obtaining samples, please contact Brooke Mossman, Mark Ellis (markellis@ima-na.org), or Michelle Wyart at EUROTALC (mwyart@ima-europe.eu).

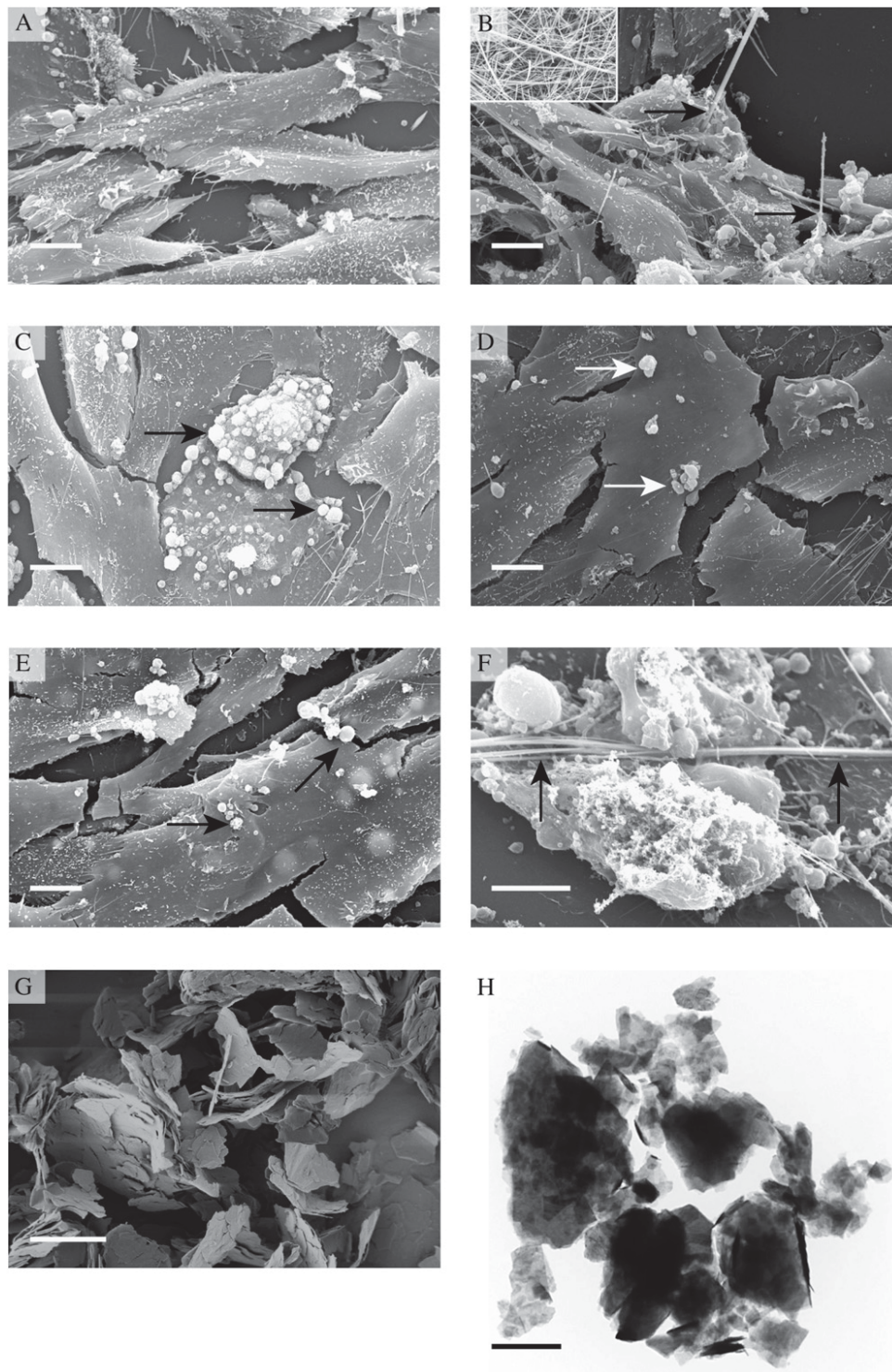


Figure 1. Interaction of fibers and particles with (A–E) LP9/TERT-1 human mesothelial cells and (F) IOSE ovarian epithelial cells after 24 hours of exposure to (B, E, F) high and (C, D) low concentrations of particulates. (G) Field emission scanning electron microscopy (FESEM) and (H) transmission electron microscopy (TEM) show structure of nonfibrous talc. (A) Morphology of unexposed near-confluent LP9/TERT-1 cells. (B) Membrane blebbing and piling up of cells in response to crocidolite asbestos (arrows). (C) Nonfibrous talc and (D) fine TiO_2 (arrows) on cell surface. (E) Single and small clumps of glass beads on plasma membrane. (F) Interaction of asbestos fibers (arrows) with IOSE cells that exhibit an exudate and membrane ruffling in response to fibers. Bars = 10 μm . (G) FESEM and (H) TEM showing morphology of platy talc bulk material. Bars = 2 μm .

Transfection of LP9 Cells with siRNA

On-Target plus Non-targeting siRNA #1 (scrambled control), and On-Target plus SMART pool human *ATF3* siRNA (100 nM; Dharmacon, Lafayette, CO) were transfected into LP9 cells at near confluence using Lipofectamine 2000 (Invitrogen, Carlsbad, CA), following the manufacturer's protocol. The efficiency of *ATF3* knockdown was determined by QRT-PCR after 48 and 72 hours.

Bio-Plex Analysis of Cytokine and Chemokine Concentrations in Medium of LP9/TERT-1 Cells

To quantify cytokine and chemokine levels in conditioned medium of cells transfected with siATF3 or scrambled control and exposed to

asbestos for 24 hours, a multiplex suspension protein array was performed using the Bio-Plex protein array system as described previously (17) and a Human Cytokine 27-plex panel (Bio-Rad, Hercules, CA). Three biological replicates were used for each treatment group.

Statistical Analysis

Data from QRT-PCR and cell viability assays were evaluated by ANOVA using the Student Neuman-Keul's procedure for adjustment of multiple pairwise comparisons between treatment groups or using the nonparametric Kruskal-Wallis and Mann-Whitney tests. Differences with P values ≤ 0.05 were considered statistically significant.

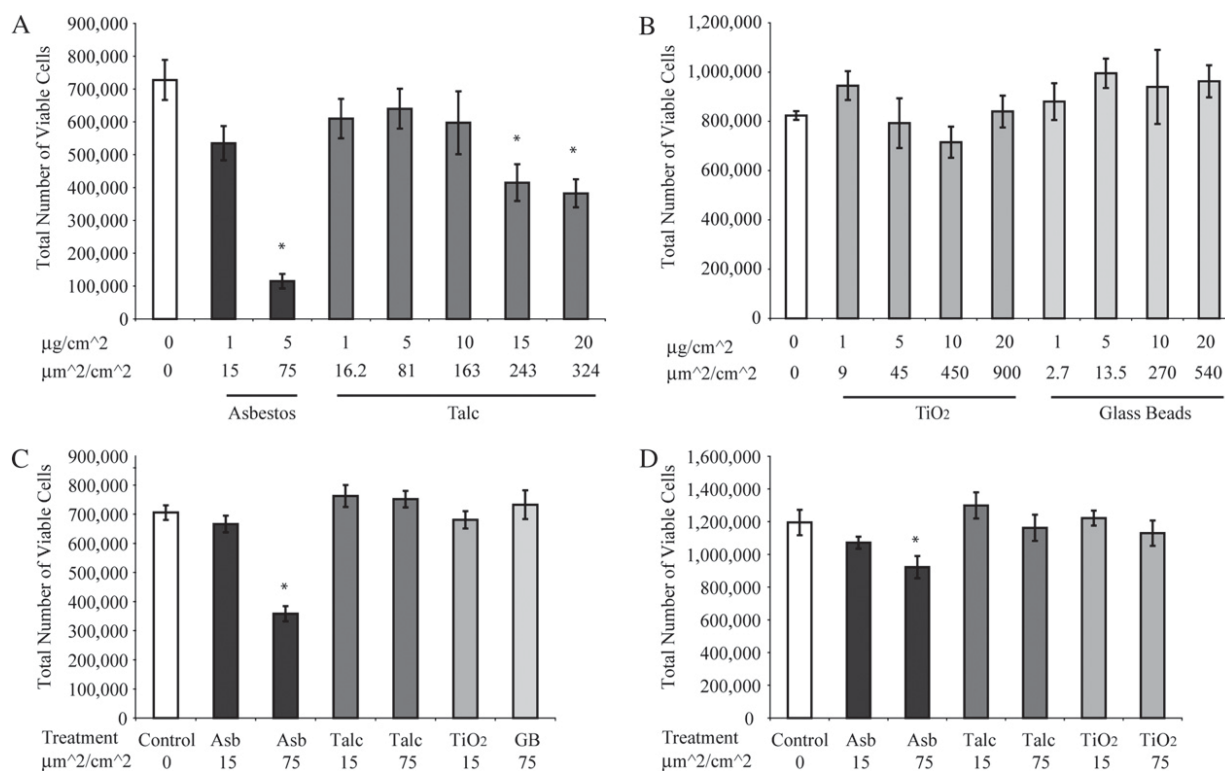


Figure 2. Cell viability after 24 hours of exposure to asbestos fibers and particles in (A–C) LP9/TERT-1 and (D) IOSE (D). Mean \pm SE of 1 (A, B) or 3 (C, D) individual experiments where $n = 3$ per group per experiment. * $P \leq 0.05$ compared with untreated (0) groups.

RESULTS

Characterization of Particulate Preparations

Table 1 shows the major chemical formulas of crocidolite asbestos fibers (defined as having a greater than 3:1 length to width ratio) and particle samples used in experiments, although trace amounts of other elements occur in the NIEHS asbestos standards (15). In addition, we examined the morphology and cellular interactions of asbestos fibers, talc, and other particles using SEM (Figure 1). These studies revealed that only high ($75 \mu\text{m}^2/\text{cm}^2$) surface area concentrations of asbestos caused membrane blebbing and other toxic manifestations in cells (Figures 1B and 1F). In contrast, particles of nonfibrous talc (Figure 1C), fine TiO_2 (Figure 1D), and glass beads (Figure 1E) were nontoxic. Both asbestos fibers and particles were observed on the cell surface and were encompassed by cells. Nonfibrous talc occurred in platy particles that were uniform in appearance as viewed by FESEM (Figure 1G) and TEM (Figure 1H).

Asbestos Fibers at High Concentrations Are Toxic to LP9/TERT-1 Human Mesothelial Cells and Less So to Ovarian Epithelial Cells in Contrast to Particle Preparations

Figure 2 shows the results of trypan blue exclusion tests in LP9/TERT-1 and IOSE cells. In LP9/TERT-1 cells (Figures 2A–2C), asbestos at high surface area concentrations ($75 \mu\text{m}^2/\text{cm}^2$) caused significant decreases (50–80%) in cell viability that were more striking than those observed in IOSE cells (Figure 2D). Nonfibrous talc at $75 \mu\text{m}^2/\text{cm}^2$ was nontoxic, and significant increases in toxicity were only achieved with addition of talc at ≥ 3 -fold higher concentrations in LP9/TERT-1 cells (Figure 2A), but not in IOSE cells (data not shown). Neither TiO_2 nor glass beads were significantly toxic to either cell type over a range of concentrations (Figure 2B).

Asbestos Fibers, but Not Particle Preparations, Cause Dose- and Time-Related Changes in Gene Expression in Human LP9 Mesothelial Cells

Figure 3 shows a summary of significantly increased or decreased (> 2 -fold compared with untreated controls) gene expression by asbestos (Figures 3A–3C) and nonfibrous talc (Figure 3D) in LP9/TERT-1 cells as well as the classification of genes by ontology. These studies revealed that gene expression changes by low concentrations of asbestos were less (29 increases) than at high concentrations (236 alterations including decreases) at 8 hours. Moreover, numbers of significant mRNA level alterations (205) at low concentrations of asbestos increased over time. In contrast, fewer numbers (30) of gene expression increases were observed at high concentrations of talc at 8 hours compared with identical surface areas of asbestos (236 changes), and no decreases in gene expression were observed. No significant alterations in gene expression were observed with low concentrations of talc at 24 hours or with TiO_2 or glass beads at either concentration or time point (data not shown). The major genes affected by asbestos or talc in LP9/TERT-1 cells are listed in Tables 2–4. This information reveals that the fold-increases in common genes expressed by asbestos-treated cells increase in a dose-related fashion at 8 hours. Although dose-responses were observed with talc at 8 hours, the numbers of significant gene increases as well as fold-increases were less than that observed with asbestos and decreased over time. Since mRNA expression of *ATF3* and *IL8* were increased by either asbestos or talc in LP9/TERT-1 cells, the increased expression of these genes was verified by QRT-PCR in mineral-exposed cells as compared with untreated control cells (Figure 4).

In NYU474 cells, QRT-PCR was used to validate that eight asbestos-induced genes in LP9 cells were up-regulated in

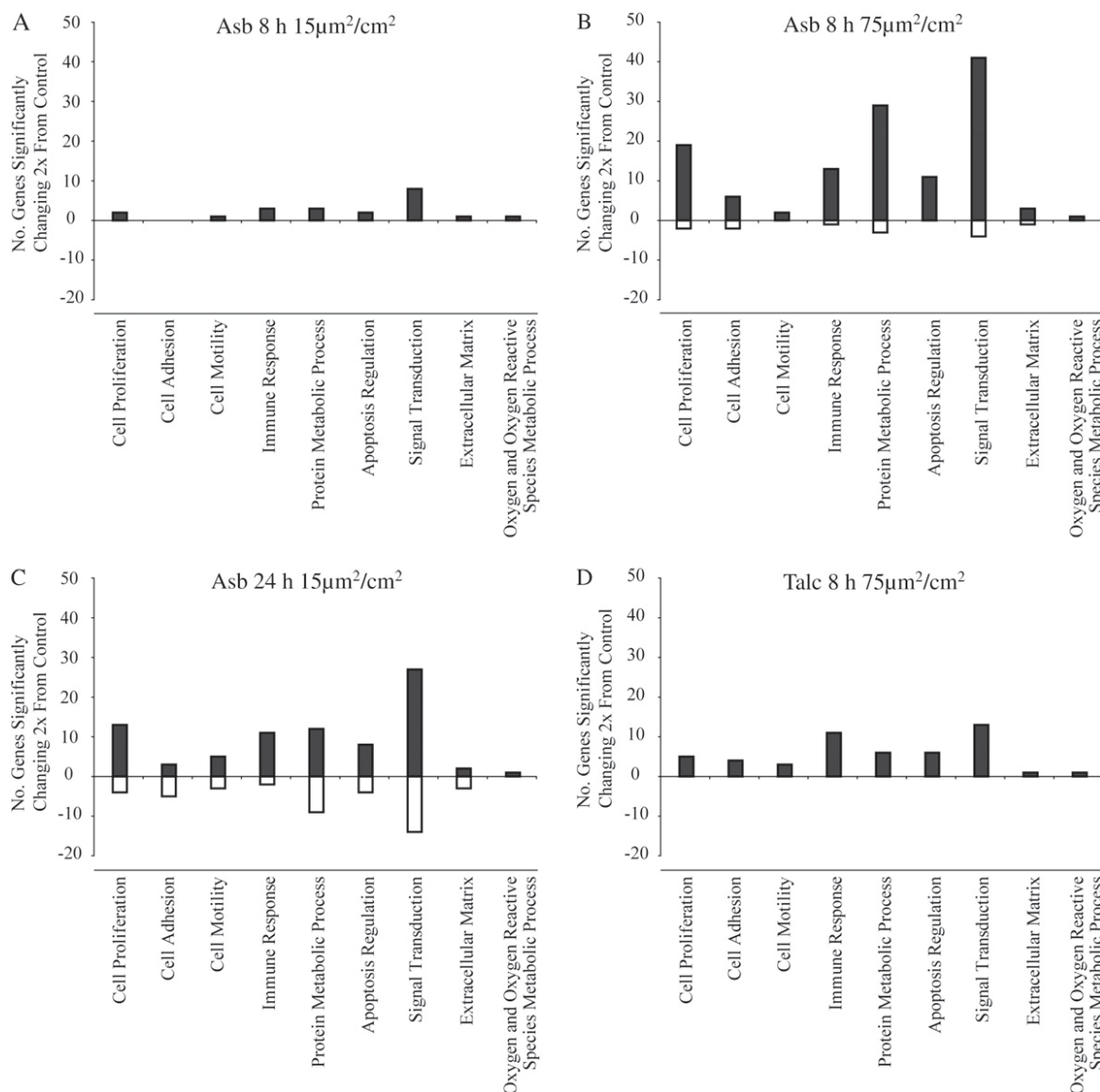


Figure 3. Numbers of changes ($P \leq 0.05$) in gene expression and classification by ontology in LP9/TERT-1 cells after exposure to (A–C) crocidolite asbestos or (D) nonfibrous talc.

normal human mesothelial cells (*ATF3*, *PTGS2* or *COX2*, *FOSB*, *IL8*, *NR4A2*, and *TFPI2*). Results showed that mRNA levels of six of the eight genes evaluated were increased in a dose-responsive fashion after exposure to asbestos for 24 hours (Figure 5).

IOSE Ovarian Epithelial Cells Exhibit Few Gene Expression Changes in Response to Asbestos

In contrast to LP9/TERT-1 and NYU474 mesothelial cells, IOSE cells showed no significant gene up-regulation or down-regulation in response to lower concentrations of asbestos at 8 or 24 hours (data not shown). At high concentrations of asbestos at 8 hours, mRNA levels of only two genes (*NR4A2* and *CXCL2* or *MIP2*) were increased in comparison to untreated IOSE cells (Table 4). At 24 hours, high concentrations of asbestos caused less than 4-fold increases in expression of only 16 genes, and decreased expression of 1 gene, *Profilin 1* (data not shown). No significant mRNA changes were observed with nonfibrous talc, fine TiO_2 or glass beads at either time point.

Inhibition of *ATF3* by siRNA Alters Asbestos-Induced Cytokines in LP9/TERT-1 Cells

Since *ATF3* was a common gene up-regulated by asbestos in mesothelial cells its functional role in cytokine production in LP9 cells was evaluated. As shown in Figure 6A, *ATF3* was successfully inhibited in LP9/TERT-1 cells using siATF3 as described in MATERIALS AND METHODS. Cells transfected with control siRNA or siATF3 were then exposed to asbestos ($75 \mu\text{m}^2/\text{cm}^2$ $n = 3$) for 24 hours, and medium was collected and analyzed for cytokines and growth factors using Bio-Plex analyses. Inhibition of *ATF3* altered levels of asbestos-induced inflammatory cytokines (IL-1 β , IL-13, G-CSF) and the growth factor (PGDF-BB) in LP9/TERT-1 cells (Figure 6B). Trends in diminishing levels of VEGF were also observed, although not statistically significant.

DISCUSSION

Gene expression analysis has been used for the classification of soluble toxicants in rodent and human cells *in vitro*. Models of

TABLE 2. TOP 10 GENES AFFECTED BY CROCIDOLITE ASBESTOS AT 8 AND 24 H IN LP9/TERT-1 HUMAN MESOTHELIAL CELLS

Concentration	Low (15 $\mu\text{m}^2/\text{cm}^2$)		High (75 $\mu\text{m}^2/\text{cm}^2$)
Time	8 h	24 h	8 h
Fold Change			
Up-regulated			
Activating transcription factor 3 (ATF3)	9	9	27
Prostaglandin-endoperoxide synthase 2 (PTGS2)	7	8	16
Superoxide Dismutase 2 (SOD2)	6	6	2
Chemokine (C-X-C motif) ligand 3 (CXCL3)	4	NC	16
FBJ murine osteosarcoma viral oncogene homolog B (FOSB)	4	NC	NC
Tissue factor pathway inhibitor 2 (TFPI2)	4	14	11
Pyruvate dehydrogenase kinase, isozyme 4 (PDK4)	3	9	15
Chemokine (C-X-C motif) ligand 2 (CXCL2)	3	NC	NC
Angiopoietin-like 4 (ANGPLT4)	3	NC	NC
Kruppel-like factor 4 (gut) (KLF4)	3	NC	NC
Interleukin 8 C-terminal variant, 211506_s_t (IL8)	NC	8	12
Interleukin 1 receptor-like 1 (IL1R1)	NC	6	11
Nuclear receptor subfamily 4 (NR4A2)	NC	NC	11
Solute carrier family 7 (SLC7A2)	NC	6	10
Pleckstrin homology-like domain (PHLDA1)	NC	7	NC
Interleukin 8 (IL8)	NC	6	NC
Down-regulated			
Inhibitor of DNA binding 3 (ID3)	NC	NC	-5
Inhibitor of DNA binding 1 (ID1)	NC	NC	-3
Cytochrome P450, family 24 (CYP24A1)	NC	NC	-3
Basic helix-loop-helix domain (BHLHB3)	NC	NC	-3
SMAD family member 6 (SMAD6)	NC	NC	-3
S-phase kinase associated protein 2 (SKP2)	NC	NC	-3
Cadherin 10, type 2 (CDH10)	NC	NC	-3
START domain containing 5 (STARD5)	NC	NC	-3
211042_x_at	NC	NC	-2
Interferon-induced protein with tetratricopeptide (IFIT1)	NC	NC	-2
Oxytocin receptor (OXTR)	NC	-6	NC
Transcribed locus	NC	-5	NC
Chromosome 5 open reading frame (C5orf13)	NC	-5	NC
Cytochrome P450, family 24 (CYP24A1)	NC	-4	NC
Chromosome 21 open reading frame (C21orf7)	NC	-3	NC
KIAA1199	NC	-3	NC
Methyltransferase like 7A (METTL7A)	NC	-3	NC
PDZ domain containing RING finger 3 (PDZRN3)	NC	-3	NC
Periplakin (PPL)	NC	-3	NC
Phospholipase-C-like 1 (PLCL1)	NC	-3	NC

Definition of abbreviation: NC, no significant ($P \leq 0.05$) change > 2-fold from control.

transcript profiling for discrimination of toxic and nontoxic compounds in liver and other organs have also been developed in rodents (18), confirming the hypothesis that predictive modeling for classification of toxic agents and carcinogens is feasible. Here we used toxicogenomic approaches in human mesothelial cells, a cell type exquisitely sensitive to asbestos (19) and human contact-inhibited ovarian epithelial cells, a cell type not linked to carcinogenesis by asbestos, to determine whether the magnitude of altered gene expression by insoluble particulates correlated with their toxicity to cells and documented pathogenicity in humans. Although a recent study has examined gene expression profiles comparatively in crocidolite asbestos-exposed human lung adenocarcinoma (A549) and SV40-immortalized bronchial (BEAS-2B) or pleural mesothelial cell lines (MET5A) by cluster analysis (20), our studies are the first to examine gene expression changes by asbestos in comparison to other well-characterized particles in a human cell line that exhibits features of normal mesothelial cells (5). Although strict comparisons between cell types are not justified because SV40 Tag was used to immortalize the IOSE ovarian epithelial cell line (6), and SV40 infection is known to decrease sensitivity of human mesothelial cell lines to toxicity by asbestos

(21), our studies suggest that the increased numbers of gene expression alterations observed in LP9/TERT-1 human mesothelial cells reflect elevated sensitivity of this cell type to asbestos. NYU474 human mesothelial cells were more resistant than LP9/TERT-1 cells to asbestos toxicity, permitting us to perform QRT-PCR studies at both concentrations of asbestos at 24 hours. These results confirmed common dose-related patterns of gene expression in mesothelial cells versus ovarian epithelial (IOSE) cells.

It is generally recognized that geometry and length and width (i.e., aspect ratio) of durable fibers such as amphibole asbestos types (crocidolite, amosite) are important properties determining toxicity, transforming potential, and carcinogenicity in rodents and humans (13, 22, 23). Since talc can occur in various geometries (nonfibrous and fibrous) and can be contaminated with other minerals, including amphiboles, in some mining deposits (reviewed in Ref. 24), we used a well-characterized, nonfibrous talc sample here to allow evaluation of a particle not causing mesotheliomas or pleural sarcomas in rodents (23). Moreover, nonfibrous talc is regarded as noncarcinogenic in humans (25). Since talc is a magnesium silicate, and Mg^{2+} may interact with negatively charged molecules on the cell surface to

TABLE 3. GENES UP-REGULATED BY NONFIBROUS TALC IN LP9/TERT-1 HUMAN MESOTHELIAL CELLS

Gene	Fold Increase
8 h Low (15 $\mu\text{m}^2/\text{cm}^2$)	
Activating transcription factor 3 (ATF3)	3
8 h High (75 $\mu\text{m}^2/\text{cm}^2$)	
Activating transcription factor 3 (ATF3)	13
Inhibin, beta A (INHBA)	9
Chemokine (C-X-C motif) ligand 3 (CXCL3)	7
Superoxide dismutase 2 (SOD2)	7
Interleukin 8 C-terminal variant, 211506_s_t (IL8)	6
Prostaglandin-endoperoxide synthase 2 (PTGS2)	5
Interleukin 8 (IL8)	5
FBJ murine osteosarcoma viral oncogene homolog B (FOSB)	5
Tumor necrosis factor alpha-induced protein 6 (TNFAIP6)	4
Tissue factor pathway inhibitor 2 (TFPI2)	4
Chemokine (C-X-C motif) ligand 2 (CXCL2)	3
Intercellular adhesion molecule 4 (CICAM4)	3
ChaC, cation transport regulator homolog 1 (ChaC 1)	3
Nuclear receptor subfamily 4, group A, member 3 (NR4A3)	3
Pleckstrin homology-like domain, family A, member 1 (PHLDA1)	3
Interleukin 6 (IL-6)	3
Phorbol -12-myristate-13-acetate-induced protein 1 (PMA1P1)	3
Oxidized low density lipoprotein (lectin-like) receptor 1 (OLR1)	3
Chemokine (C-C motif) ligand 20 (CCL20)	3
v-maf musculoaponeurotic fibrosarcoma oncogene homolog F	3
Interleukin 1, alpha (IL-1 α)	2
Tumor necrosis factor- α induced protein 3 (TNFAIP3)	2
Interleukin 1 receptor-like 1 (IL1RL1)	2
Angiopoietin-like 4 (ANGPLT4)	2
Kruppel-like factor 4 (KLF4)	2
GTP binding protein overexpressed in skeletal muscle (GEM)	2
Pentraxin-related gene, rapidly induced by IL-1 beta (PTX3)	2
Interleukin 1 beta (IL-1 β)	2
HSPB (heat shock 27 kD) associated protein 1 (HSPBAP1)	2
Kynureninase (KYNU)	2

disturb cell homeostasis (reviewed in Ref. 26), this may explain the few mRNA expression increases that were observed initially with talc at 8 hours. However, these changes were not observed at 24 hours, suggesting that human mesothelial cells adapt to or undergo repair after exposure to this mineral.

Our gene profiling data here and in inhalation studies using chrysotile asbestos (14) also support the concept that fine TiO_2 is nontoxic and nonpathogenic to mesothelial or other cell

TABLE 4: GENES UPREGULATED BY CROCIDOLITE ASBESTOS IN IOSE HUMAN OVARIAN CELLS

Gene	Fold increase
8 h High (75 $\mu\text{m}^2/\text{cm}^2$)	
Nuclear receptor subfamily 4 (NR4A2)	4
Chemokine (C-X-C motif) ligand 2 (MIP2)	2
24 h High (75 $\mu\text{m}^2/\text{cm}^2$)	
Nuclear receptor subfamily 4 (NR4A2)	4
DNA-damage-inducible transcript 3 (DDIT3)	3
Stromal cell-derived factor 2-like 1 (SDF2L1)	3
Heat shock 70 kD protein 1A (HSPA1A)	3
DnaJ (Hsp40) homolog, subfamily C (DNAJC3)	2
Paraspeckle component 1	2
Heat shock 70 kD protein 1B (HSPA1B)	2
Homocysteine-inducible, endoplasmic reticulum stress-inducible, ubiquitin-like domain member (HERPUD1)	2
Serum/glucocorticoid regulated kinase family, member 3 (SKG3)	2
DnaJ (Hsp40) homolog, subfamily B, member 9 (DNAJB9)	2
Arginine-rich, mutated in early stage tumors (ARMET)	2
Syntaxin 1A (brain) (STX1A)	2
Heat shock 70 kD protein 5 (HSPA5)	2
ADAM metalloproteinase with thrombospondin type 1 motif	2
Heat shock protein 90kDa beta (Grp94), member 1 (HSP90B1)	2

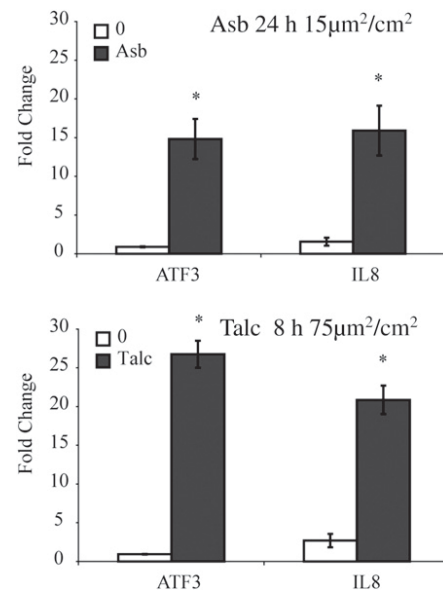


Figure 4. QRT-PCR confirms significant increases in *ATF3* and *IL8* expression by crocidolite asbestos at low concentrations and non-fibrous talc at high concentrations in LP9/TERT-1 mesothelial cells. * $P < 0.05$ as compared to untreated (0) groups.

types. Likewise, in the rat, inhalation of fine TiO_2 (defined as particles $> 0.1 \mu\text{m}$ in diameter), in contrast to ultrafine (particles $< 0.1 \mu\text{m}$ in diameter) does not give rise to predictive markers of toxicity, inflammation, pulmonary fibrosis, or oxidative stress, as indicated by elevated levels of Mn-containing superoxide dismutase (*SOD2*) in cells from bronchopulmonary lavage (27). The increased reactivity and toxicity of ultrafine particles as compared with larger fine or coarse particles have also been confirmed in a number of *in vitro* and *in vivo* experiments and is often attributed to their increased surface area and/or ability to penetrate lung cells.

Our studies reveal a number of novel genes induced by asbestos in LP9/TERT-1 cells. As previously described in a lung epithelial cell line (C10) or mouse lungs after inhalation of crocidolite asbestos (28), increases in expression of the early response gene, *FOSB*, that encodes a dimer of the activator protein-1 transcription factor, were seen. Increases in expression of several other genes linked to cell signaling proteins and transcription factor activation were observed in asbestos-exposed cells, including *NR4A2* and *PDK4*. A novel gene up-regulated at all time points and concentrations of asbestos or talc in human mesothelial cells was activating transcription factor 3 (*ATF3*), a member of the cAMP-responsive element-binding (CREB) transcription factor family that encodes two different isoforms leading to repression or activation of genes. Silencing of *ATF3* in the present study by siRNA significantly altered expression of a number of asbestos-induced inflammatory cytokines and growth factors documented in malignant mesotheliomas (29, 30). In support of our results here, other studies using *ATF3*-deficient mice and *in vitro* approaches have shown that *ATF3* is a negative regulator of pulmonary inflammation, eosinophilia, and airway responsiveness (31). Moreover, *ATF3* also negatively regulates IL-6 gene transcription in an NF- κ B model of up-regulation using melanoma cells (32). In addition, trends in production of VEGF, a known important angiogenic peptide and independent prognostic factor in human mesotheliomas (33), were observed. We have recently shown that an extracellular signal-related

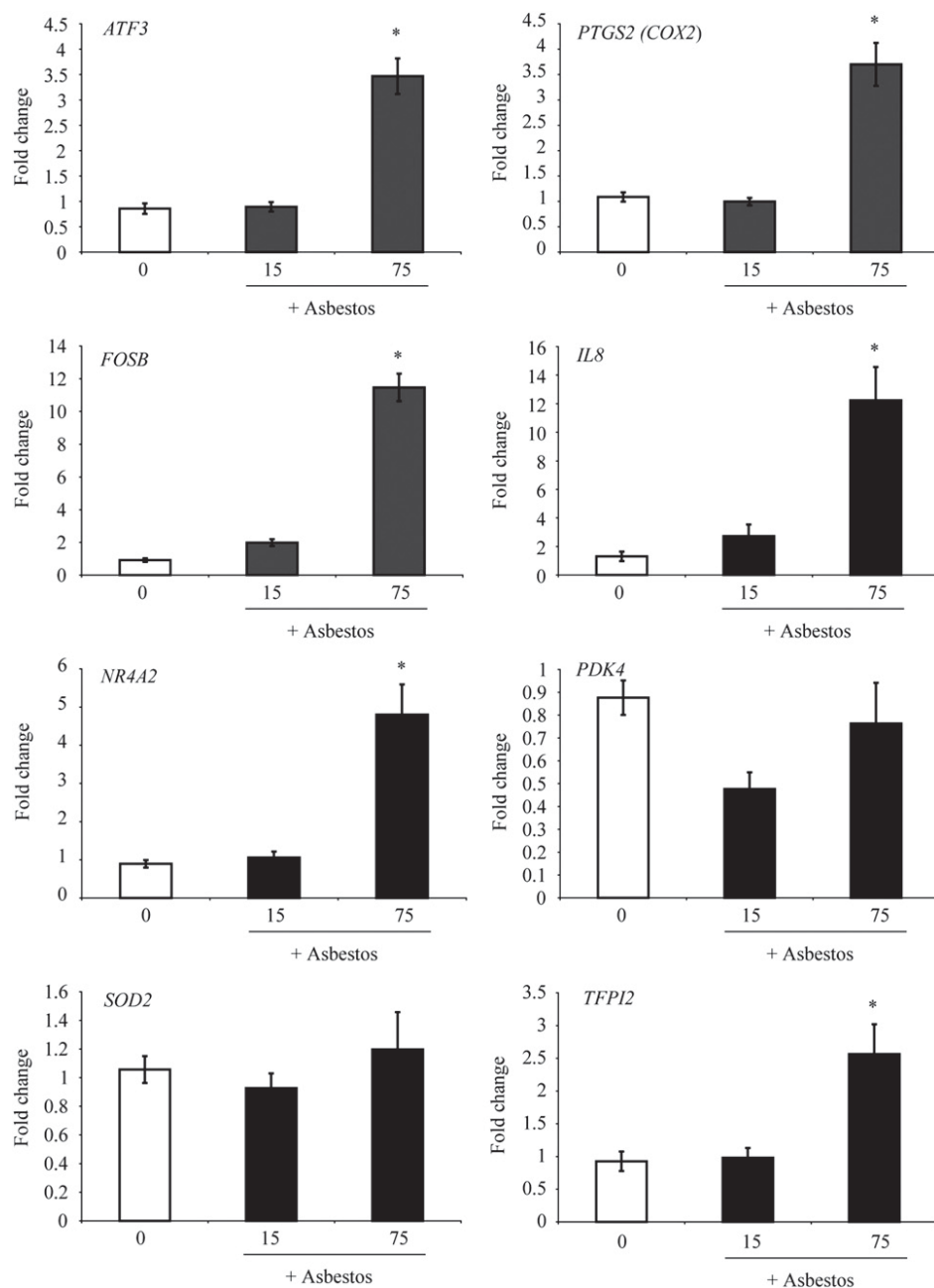


Figure 5. QRT-PCR confirms that human primary pleural mesothelial cells (NYU474) show similar patterns of asbestos-induced gene expression when compared with LP9/TERT-1 mesothelial cells. NYU474 cells were exposed to crocidolite asbestos (15 or 75 $\mu\text{m}^2/\text{cm}^2$) for 24 hours and cDNA was used for QRT-PCR. * $p \leq 0.05$ as compared with untreated cells (0).

CREB pathway in C10 lung epithelial cells modulates apoptosis after asbestos exposure (34), and recent studies are focusing on the effects of silencing *CREB* or *ATF3* on other functional and phenotypic changes in human mesothelial and mesothelioma cells (A. Shukla and colleagues, unpublished data).

Several other genes up-regulated by talc at 8 hours or affected by asbestos at both 8 and 24 hours may be important in repair from mineral-induced responses. For example, *SOD2* (Mn-containing superoxide dismutase) is an antioxidant protein occurring in the mitochondria, a target cell organ of asbestos-induced apoptosis (35). *PTGS2* (prostaglandin-endoperoxide synthase or cyclooxygenase) is a key enzyme in prostenoid biosynthesis associated with modulation of mitogenesis and inflammation. More recently, this pathway has been explored after interaction of ultrafine particles with alveolar macrophages (9). *ANG PTL4* (angiopoietin-4) encodes a serum hormone directly involved in regulating glucose homeostasis and lipid metabolism and is an apoptosis survival factor for vascular endothelial cells. The up-regulation of angio-

poietin-4 is also thought to play a role in inhibition of tumor cell motility and metastasis. *KLF4* (Kruppel-like factor 4) is a negative regulator of cell proliferation and can be a positive or negative modulator of DNA transcription.

Increased expression of genes encoding different cytokines/chemokines (i.e., *IL8*) and their receptors or ligands (e.g., IL-8 C-terminal variant, *IL1R1*, *CXCL2* or *MIP2*, *CXCL3*, and *TFP12*) by asbestos or talc suggests that the mesothelial cell also may play a role in chemotaxis, inflammation, and blood coagulation. A number of gene expression changes by asbestos also support the hypothesis that this fibrous mineral affects calcium-dependent processes including related protein kinase cascades, cell adhesion, and protein/lipid metabolism (Table 2). Although numbers of changes were more modest in IOSE cells, with the exception of *NR4A2* and *CXCL2*, a unique subset of genes was induced by asbestos in this cell type (Table 4).

Results of work here suggest that transcriptional profiling can be used to reveal molecular events by mineral dusts that are

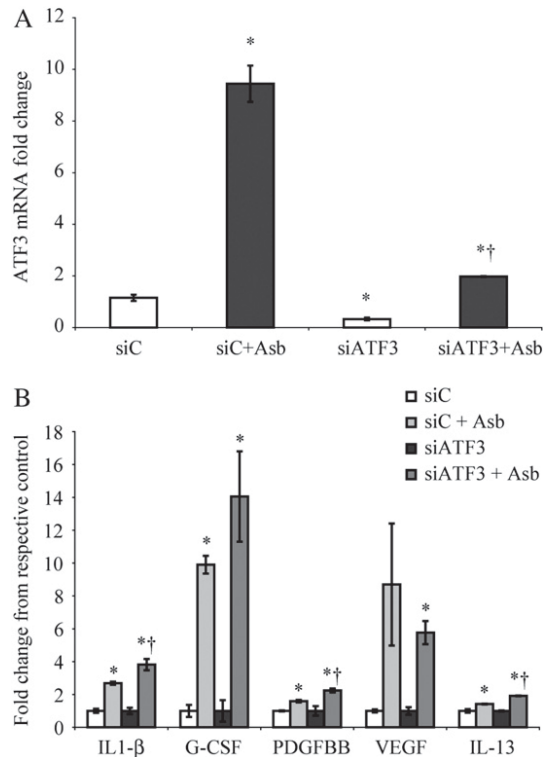


Figure 6. ATF3 inhibition using siRNA approaches alters asbestos-induced production of inflammatory cytokines and growth factors. (A) LP9/TERT-1 cells transfected with siATF3 show significant inhibition of ATF3 mRNA levels (untreated control [siC] versus siATF3 and asbestos-treated [siC Asb versus siATF3 Asb] groups). * $P \leq 0.05$ as compared with siC; † $P \leq 0.05$ as compared with siC Asb group. (B) siATF3 altered asbestos-induced cytokine levels as detected in medium at 24 hours using Bio-Plex analyses. * $P \leq 0.05$ as compared with control groups (siC and siATF3), respectively; † $P \leq 0.05$ as compared with asbestos-exposed scrambled control group (siC).

predictive of their pathogenicity in mesothelioma. Moreover, they reveal early and novel gene responses, including calcium-dependent transcription factors and antioxidant enzymes that may be pursued for their functional significance using RNA silencing or other approaches.

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References

- Mossman BT, Gee JB. Asbestos-related diseases. *N Engl J Med* 1989; 320:1721–1730.
- Mossman BT, Churg A. Mechanisms in the pathogenesis of asbestosis and silicosis. *Am J Respir Crit Care Med* 1998;157:1666–1680.
- Robinson BW, Lake RA. Advances in malignant mesothelioma. *N Engl J Med* 2005;353:1591–1603.
- Mossman BT, Bignon J, Corn M, Seaton A, Gee JB. Asbestos: scientific developments and implications for public policy. *Science* 1990;247: 294–301.
- Dickson MA, Hahn WC, Ino Y, Ronfard V, Wu JY, Weinberg RA, Louis DN, Li FP, Rheinwald JG. Human keratinocytes that express hTERT and also bypass a p16(INK4a)-enforced mechanism that limits life span become immortal yet retain normal growth and differentiation characteristics. *Mol Cell Biol* 2000;20:1436–1447.

- Choi JH, Choi KC, Auersperg N, Leung PC. Overexpression of follicle-stimulating hormone receptor activates oncogenic pathways in pre-neoplastic ovarian surface epithelial cells. *J Clin Endocrinol Metab* 2004;89:5508–5516.
- Merritt MA, Green AC, Nagle CM, Webb PM. Talcum powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer. *Int J Cancer* 2008;122:170–176.
- Mossman BT, Shukla A, Fukagawa NK. Highlight Commentary on “Oxidative stress and lipid mediators induced in alveolar macrophages by ultrafine particles”. *Free Radic Biol Med* 2007;43:504–505.
- Beck-Speier I, Dayal N, Karg E, Maier KL, Schumann G, Schulz H, Semmler M, Takenaka S, Stettmaier K, Bors W, et al. Oxidative stress and lipid mediators induced in alveolar macrophages by ultrafine particles. *Free Radic Biol Med* 2005;38:1080–1092.
- Oberdorster G, Ferin J, Gelein R, Soderholm SC, Finkelstein J. Role of the alveolar macrophage in lung injury: studies with ultrafine particles. *Environ Health Perspect* 1992;97:193–199.
- Brown DM, Wilson MR, MacNee W, Stone V, Donaldson K. Size-dependent proinflammatory effects of ultrafine polystyrene particles: a role for surface area and oxidative stress in the enhanced activity of ultrafines. *Toxicol Appl Pharmacol* 2001;175:191–199.
- Donaldson K, Tran CL. Inflammation caused by particles and fibers. *Inhal Toxicol* 2002;14:5–27.
- Health Effects Institute - Asbestos Research. Asbestos in public and commercial buildings: a literature review and synthesis of current knowledge. Cambridge, MA: The Health Effects Institute; 1991.
- Sabo-Attwood T, Ramos-Nino M, Bond J, Butnor KJ, Heintz N, Gruber AD, Steele C, Taatjes DJ, Vacek P, Mossman BT. Gene expression profiles reveal increased mClna3 (Gob5) expression and mucin production in a murine model of asbestos-induced fibrogenesis. *Am J Pathol* 2005;167:1243–1256.
- Campbell WJ, Huggins CW, Wylie AG. Chemical and physical characterization of amosite, chrysotile, crocidolite, and nonfibrous tremolite for oral ingestion studies Washington, DC: National Institute of Environmental Health Sciences; 1980. No. 8542.
- Blumen SR, Cheng K, Ramos-Nino ME, Taatjes DJ, Weiss DJ, Landry CC, Mossman BT. Unique uptake of acid-prepared mesoporous spheres by lung epithelial and mesothelioma cells. *Am J Respir Cell Mol Biol* 2007;36:333–342.
- Shukla A, Lounsbury KM, Barrett TF, Gell J, Rincon M, Butnor KJ, Taatjes DJ, Davis GS, Vacek P, Nakayama KI, et al. Asbestos-induced peribronchiolar cell proliferation and cytokine production are attenuated in lungs of protein kinase C-delta knockout mice. *Am J Pathol* 2007;170:140–151.
- Steiner G, Suter L, Boess F, Gasser R, de Vera MC, Albertini S, Ruepp S. Discriminating different classes of toxicants by transcript profiling. *Environ Health Perspect* 2004;112:1236–1248.
- Lechner JF, Tokiwa T, LaVeck M, Benedict WF, Banks-Schlegel S, Yeager H Jr, Banerjee A, Harris CC. Asbestos-associated chromosomal changes in human mesothelial cells. *Proc Natl Acad Sci USA* 1985;82:3884–3888.
- Nymark P, Lindholm PM, Korpela MV, Lahti L, Ruosaari S, Kaski S, Hollmen J, Anttila S, Kinnula VL, Knuutila S. Gene expression profiles in asbestos-exposed epithelial and mesothelial lung cell lines. *BMC Genomics* 2007;8:62.
- Cacciotti P, Barbone D, Porta C, Altomare DA, Testa JR, Mutti L, Gaudino G. SV40-dependent AKT activity drives mesothelial cell transformation after asbestos exposure. *Cancer Res* 2005;65:5256–5262.
- Davis JM, Addison J, Bolton RE, Donaldson K, Jones AD, Smith T. The pathogenicity of long versus short fibre samples of amosite asbestos administered to rats by inhalation and intraperitoneal injection. *Br J Exp Pathol* 1986;67:415–430.
- Stanton MF, Layard M, Tegeris A, Miller E, May M, Morgan E, Smith A. Relation of particle dimension to carcinogenicity in amphibole asbestos and other fibrous minerals. *J Natl Cancer Inst* 1981;67:965–975.
- Guthrie GD Jr, Mossman BT. Health effects of mineral dusts. Washington, DC: Mineralogical Society of America; 1993.
- IARC. Silica and some silicates. *IARC Monogr Eval Carcinog Risk Chem Hum* 1987;42:185.
- Mossman B, Light W, Wei E. Asbestos: mechanisms of toxicity and carcinogenicity in the respiratory tract. *Annu Rev Pharmacol Toxicol* 1983;23:595–615.
- Janssen YM, Heintz NH, Mossman BT. Induction of c-fos and c-jun proto-oncogene expression by asbestos is ameliorated by N-acetyl-L-cysteine in mesothelial cells. *Cancer Res* 1995;55:2085–2089.

28. Ramos-Nino ME, Heintz N, Scappoli L, Martinelli M, Land S, Nowak N, Haegens A, Manning B, Manning N, MacPherson M, *et al.* Gene profiling and kinase screening in asbestos-exposed epithelial cells and lungs. *Am J Respir Cell Mol Biol* 2003;29:S51–S58.
29. Yoshimoto A, Kasahara K, Saito K, Fujimura M, Nakao S. Granulocyte colony-stimulating factor-producing malignant pleural mesothelioma with the expression of other cytokines. *Int J Clin Oncol* 2005;10:58–62.
30. Vogelzang NJ, Herndon JE II, Miller A, Strauss G, Clamon G, Stewart FM, Aisner J, Lyss A, Cooper MR, Suzuki Y, *et al.* High-dose paclitaxel plus G-CSF for malignant mesothelioma: CALGB phase II study 9234. *Ann Oncol* 1999;10:597–600.
31. Gilchrist M, Henderson WR Jr, Clark AE, Simmons RM, Ye X, Smith KD, Aderem A. Activating transcription factor 3 is a negative regulator of allergic pulmonary inflammation. *J Exp Med* 2008;205:2349–2357.
32. Karst AM, Gao K, Nelson CC, Li G. Nuclear factor kappa B subunit p50 promotes melanoma angiogenesis by upregulating interleukin-6 expression. *Int J Cancer* 2009;124:494–501.
33. Demirag F, Unsal E, Yilmaz A, Caglar A. Prognostic significance of vascular endothelial growth factor, tumor necrosis, and mitotic activity index in malignant pleural mesothelioma. *Chest* 2005;128:3382–3387.
34. Barlow CA, Barrett TF, Shukla A, Mossman BT, Lounsbury KM. Asbestos-mediated CREB phosphorylation is regulated by protein kinase A and extracellular signal-regulated kinases 1/2. *Am J Physiol Lung Cell Mol Physiol* 2007;292:L1361–L1369.
35. Shukla A, Stern M, Lounsbury KM, Flanders T, Mossman BT. Asbestos-induced apoptosis is protein kinase C delta-dependent. *Am J Respir Cell Mol Biol* 2003;29:198–205.